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**Synthesis and Properties of Amino Acid-derived
Optically Active Polymers**

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2009

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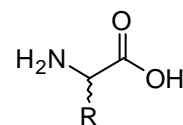
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General Introduction

Research Background

Although α -amino acids are simple molecules with the structure of $\text{H}_2\text{NCHRCOOH}$, they have multiple functional groups such as hydroxy and mercapto groups as well as amino and carboxy groups, which enable them to be transformed into a



R = alkyl group,
carboxy group,
amino group,
mercapto group...

wide variety of optically active materials. Therefore they are regarded as inexpensive and highly pure chiral sources which have broad utility for organic chemistry. Due to their high reactivity, they are employed for a wide range of applications such as toiletries, smoothing agents, waste oil treatment agents, antioxidant agents, and surface preparation agents of metals as well as pharmaceutical drugs, food, and surfactants.¹ Amino acid derivatives including proline derivatives, which have been reported as safe and effective catalysts for aldol reaction,^{2a} have also attracted much attention as highly active asymmetric organocatalysts for various reactions.²

Besides, polypeptides synthesized from amino acids have been examined as models of proteins, and they are indispensable compounds for our life. They have expanded properties, which are inimitable for synthetic macromolecules; electron transfer, information transfer, photo reactivity, selective catalytic function, and so on. In addition, it is noted that polypeptides take higher order structures such as α -helix, β -sheet, bend, and random coil dependent on the constituent amino acids. Catalysis for various reactions utilizing their higher order structures has been also reported.³

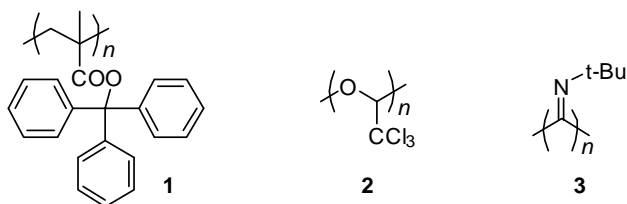
The attempt to incorporate amino acids into polymers has also been performed by taking advantage of their high reactivity. These peptide-mimetic polymers are expected to show biocompatibility and biodegradability in a fashion similar to naturally derived biopolymers, and have been investigated for applications such as a drug delivery system.⁴ Polymers showing multifunction and high performance have

been developed based on the transformation of their higher order structures in response to the external stimuli such as temperature and pH. The research background of this doctoral thesis includes the topics of helical polymers, substituted helical polyacetylenes, acyclic diene metathesis, diketopiperazine, and asymmetric organocatalyst. They are introduced in detail in the following sections.

Helical Polymers. Helix is the most fundamental conformation among the higher order structures of macromolecules, and has chirality originating from the conformation. They are often observed in biomacromolecules such as DNA, protein and so on.⁵ These helical polymers, whose screw senses are predominantly one-handed, and supramolecules formed by helical polymers play an important role to express the essential function for the process of a living organisms such as *in vivo* exquisite reactions, molecular recognition, and replication. Appropriate control of the secondary structure can not only improve the performances of the function, but also construct advanced synthetic polymers to which various functions are provided.

The history of helical polymers is old and dates back to the research about α -amylose by Hanes in 1937.⁶ Thereafter, three remarkable discoveries about the helical structure of polymers, all of which won Nobel prize, were made in the 1950s. They are α -helix of polypeptide (Pauling, in 1951),⁷ the double helix of DNA (Watson and Crick, in 1953),⁸ and 3/1 helix of isotactic polypropylene (Natta, in 1955).⁹ Especially the elucidation of helical structure of isotactic polypropylene in the solid state suggests that the precise control of tacticity makes it possible to construct helical synthetic polymers. In the next half of century, various types of artificial helical polymers have been synthesized. These helical polymers are classified into two categories by their properties and characters of the helix, i.e., stable helix, which is stably-kept even in solution, and dynamic helix, whose helical senses invert constantly

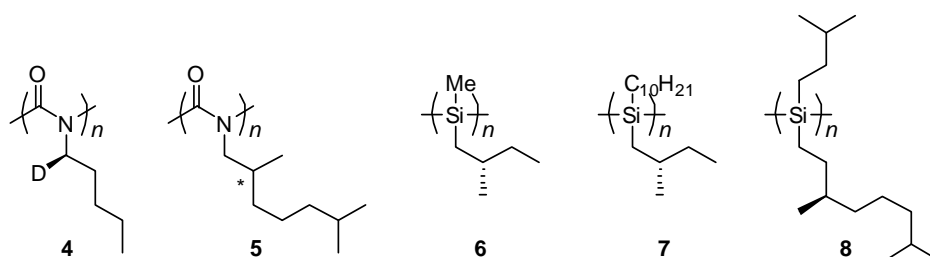
due to the small energetic barriers for helix reversal.



Poly(alkyl methacrylate) (**1**),¹⁰ polychloral (**2**),¹¹ and polyisocyanide (**3**),¹² which have very bulky substituents, are taken for representative examples of stable helix. The rigidity of the main chain and/or the steric repulsion of the bulky pendant groups avoid helix-helix or helix-coil transformations. Isotactic **1** is obtained by asymmetric anionic polymerization by using *n*-BuLi with (–)-sparteine or optically active alkyl lithium, and takes completely one-handed helical conformation, which is stabilized by steric repulsion of bulky side chains. **1** is used as a chiral stationary phase for high performance liquid chromatography (HPLC),¹³ and applied to the separation of various racemic compounds including medicinal drugs. This is the first example of an artificial helical polymer put to practical use. However, it has the disadvantage that the ester groups in the side chains are easily hydrolyzed by alcohol used as an eluent. Recently, perfectly isotactic polymethacrylamide which takes predominantly one-handed helical structure has been synthesized by asymmetric radical polymerization using optically active menthol as a part of polymerization solvents.¹⁴ Durability for solvolysis is improved dramatically by the modification of ester linkage to amide one, and so it is expected to be used practically as a chiral stationary phase. Polychloral **2** is obtained as an isotactic polymer by asymmetric anionic polymerization of trichloroacetaldehyde (chloral) using optically active lithium alkoxide, and takes a stable 4/1 helical conformation.¹¹ It is also employed for an HPLC stationary phase, and can resolve the racemates of aromatic compounds.¹⁵

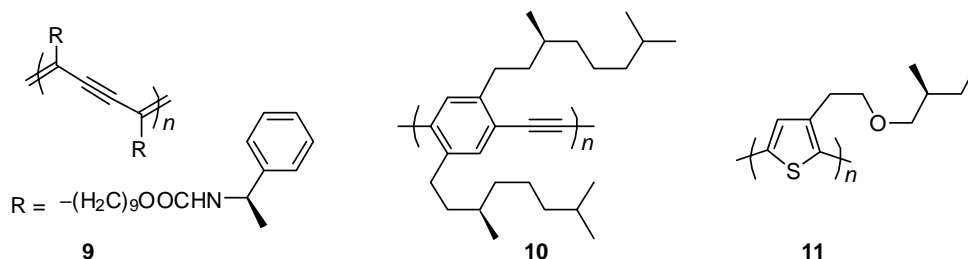
Polyisocyanide **3**, whose main chain all consists of imino groups, is obtained by polymerization using a nickel catalyst, and forms a 4/1 helix by the steric repulsion between the side chains.¹² It can take a pillar shape in which pendant groups regularly locate in the 4 directions around the 4/1 helical backbone. Recently, introduction of functional molecules such as porphyrin,¹⁶ ferrocene,¹⁷ and so on¹⁸ at the ordered position of the helix have been examined for alignment of them.

On the other hand, typical examples of dynamic helical polymers include polyisocyanates and polysilanes. They possess the rigid main chain and the long helical persistence length. Their helical senses are determined by the chiral substituents kinetically, and polymers obtained from optically inactive monomers exist as an equivalent mixture of right- and left-handed helical structures. Polyisocyanates carrying chiral pendant groups have been reported by Goodman and Chen,¹⁹ and then Green have reported that **4**, whose chirality is only based on the difference between H and D in the pendant groups, forms a predominantly one-handed helical structure.²⁰ Moreover, chiral-achiral copolymerization suggests that the screw sense is determined efficiently by only a small amount of chiral units (sergeants-and-soldiers rule).²¹ In a similar fashion, *R-S* copolymerization (**5**) reveals that the minority enantiomer of the side chain fits into the helix sense preferred by the majority enantiomer (majority rule).²² Polysilanes (**6–8**), which are also dynamic helical polymers, have Si σ -conjugating main chains, allowing the conformational study by means of photo-physical analysis of the polymers.²³ The absorption wavelength (λ_{\max}) of CD and UV-vis spectra has close relations with the torsional angle of the main chain.



Polymers with 7/3 helical structure display λ_{\max} at around 320 nm, while those with 2/1 helical structure show λ_{\max} at 370 nm. It has been reported that there is a proportionality relationship between the viscosity index of Mark-Houwink-Sakurada plot (α) and λ_{\max} of the polymer.^{23e}

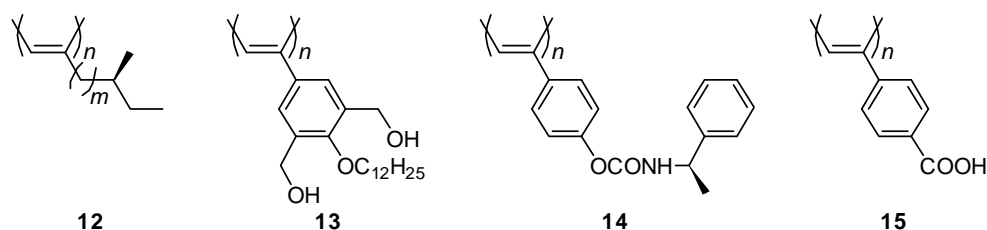
Some helical polymers such as polydiacetylenes (**9**), poly(phenyleneethynylene) (**10**), and polythiophene (**11**) show chirality based on not only the twist of the main chain as mentioned above but also the intermolecular aggregation in the solid state and in poor solvent. Because they can not aggregate in good solvent, they do not take helical but random conformation.



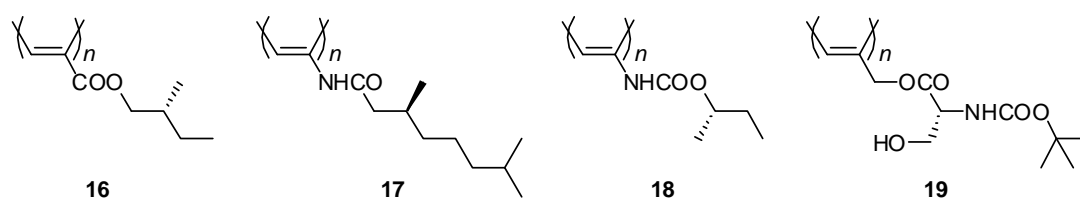
Helical Substituted Polyacetylenes. Optically active conjugated polymers are very interesting from the viewpoint of their unique photo- and electronic functions based on the helical main chain.²⁷ Therefore, they are potentially useful in areas such as electrodes for asymmetric electrosyntheses, polarized photo- and electroluminescent materials, polarization-sensitive electrooptical materials, read- and writeable materials for recording, and so on. Substituted polyacetylenes are the most typical and basic π -conjugated polymers.²⁸ Not only early transition metals but also late transition metals are used as the catalysts for polymerization of substituted acetylenes.²⁹ Recently, especially rhodium catalysts have attracted much attention, because of a wide range of application of monomers having various pendant groups due to their stability and tolerance for polar functional groups, and their cis stereochemistry of the

main chain of the resultant polymers.

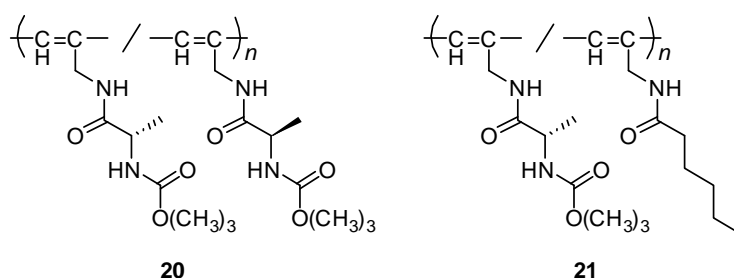
The helical conformation of polyacetylene derivatives bearing chiral side chains (**12**) has been first pointed out by Ciardelli and coworkers in 1974.³⁰ They have reported that optically active poly(1-alkyne)s prepared by an iron catalyst take primary structure with alternate double bonds along the main chain. Grubbs and coworkers have demonstrated that optically active polyacetylene derivatives can be obtained by ring opening metathesis polymerization of the corresponding cyclooctatetraene derivatives.³¹ Subsequently, helical polyacetylenes have been extended and more clearly demonstrated by Aoki in 1993^{32a} and by Yashima and Okamoto in 1994.^{33a} They have studied the chiroptical properties of rhodium-based poly(phenylacetylene)s (**13–15**).^{32, 33} These polymers have showed very high molar ellipticity at the absorption region of the main chain in the CD spectrum, suggesting that the main chains take helical conformations.



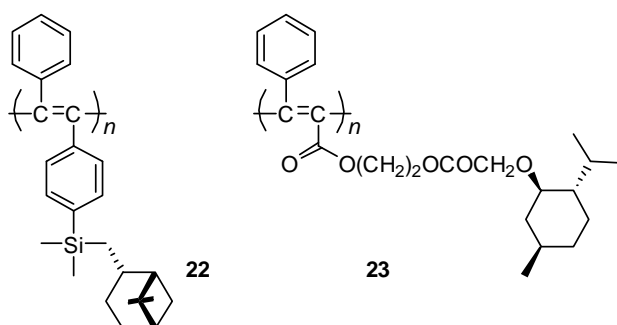
Masuda and coworkers have reported a series of helical polyacetylenes bearing pendant chiral groups. Optically active poly(propionic ester)s (**16**) exhibit large Cotton effects due to the helix formation.³⁴ They have also reported that stereoregular poly(*N*-propargylamide)s (**17**) biomimetically form helices stabilized by intramolecular hydrogen bonding along with steric repulsion.³⁵ The polymers change



the conformation by external stimuli such as heat and addition of polar solvents. The *cis*-stereoregular poly(*N*-propargylcarbamate)s³⁶ (**18**) and a serine-based poly(propargyl ester) with free hydroxyl groups³⁷ (**19**) also take helical conformations stabilized by intramolecular hydrogen bonding between the side chains in a manner similar to poly(*N*-propargylamide)s. They have determined the screw sense of substituted polyacetylenes by the exciton chirality method using stereoregular poly(*N*-propargylamide)s carrying porphyrin moieties.^{35e} It suggests that the porphyrin units in the side chains take right-handed strands, while the main chain left-handed. They have also revealed that the copolymers of alanine-based *N*-propargylamide (**20**, **21**) obey majority rule and sergeants and soldiers rule proposed by Green and coworkers.^{35f}

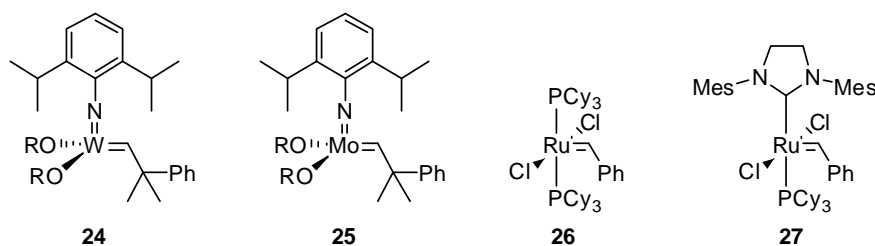


As well as monosubstituted acetylene polymers, disubstituted acetylene polymers carrying bulky pendant groups (**22**, **23**) also have been synthesized by polymerization using early transition metals such as niobium, tantalum, molybdenum, and so on. It has been reported that they form predominantly one-handed helical structures in solution.³⁸



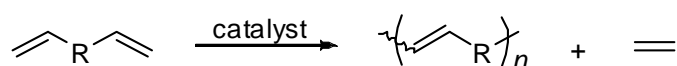
Acyclic Diene Metathesis (ADMET). As described above, various transition metal complexes are used for polymerization of substituted acetylenes. Polymerization by tantalum and molybdenum proceeds through metathesis mechanism. Metathesis is the reaction that induces redistribution of carbon-carbon double bonds between two olefins via metallacyclobutane, which is formed by coordination of a metal carbene and an olefin.

Tungsten and molybdenum complexes (**24**, **25**) have been used for metathesis reactions.³⁹ They have high catalytic activity, but suffer undesirable sensitivity for functional groups, which makes it difficult to take the substrates having the ester and amide groups within a molecule. Recently, Grubbs and coworkers have developed the ruthenium complexes (**26**, **27**) which show exquisite tolerance towards functional groups along with high activity.⁴⁰ They enable to perform metathesis reactions of the substrates with various polar groups in polar solvents such as alcohols and water, leading to extending the scope of the available substrates.

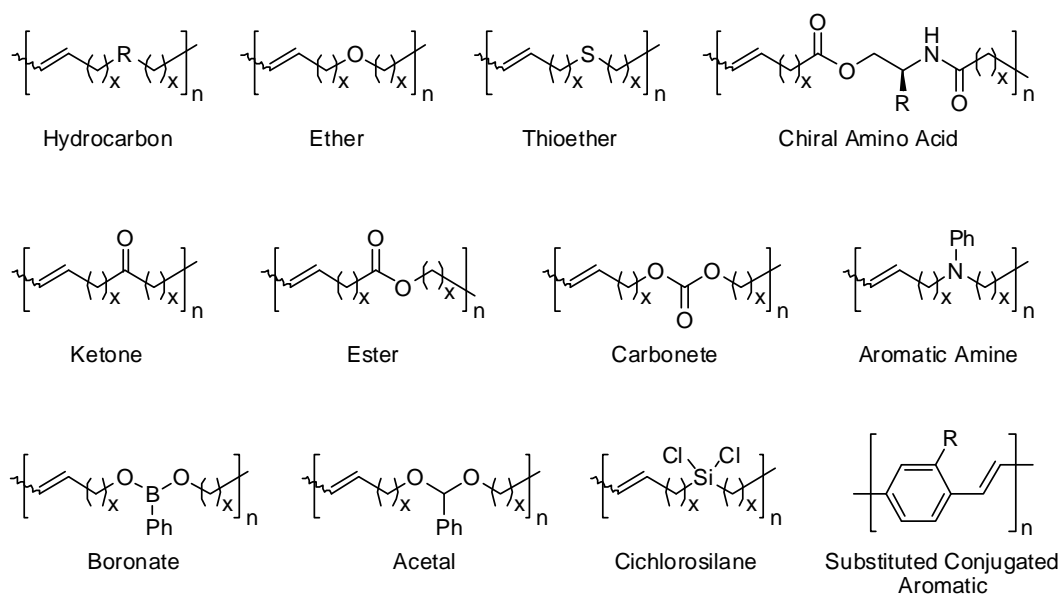


There are two methods of olefin metathesis polymerization: ring-opening metathesis polymerization (ROMP) and acyclic diene metathesis (ADMET) polymerization. ADMET polymerization is performed on α,ω -dienes to produce strictly linear polymers with unsaturated polyethylene backbones.⁴¹ ADMET is a step-growth polycondensation reaction that is driven by the removal of a small molecule, or condensate. Several features of this mechanism differentiate ADMET

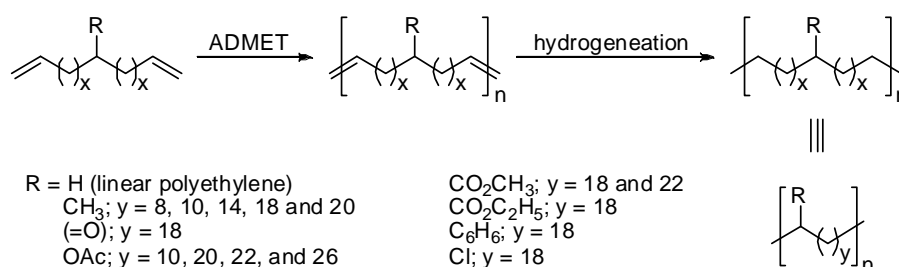
from its chain polymerization relative, ROMP. Development of highly active catalysts has provided various types of polymers and polymer architectures which are not available by the other methods than ADMET.



A wide variety of polymers have been synthesized recently by Wagener and coworkers.⁴² The functional groups of these polymers are built into the main chain of polyolefin regularly. In addition, they have synthesized the polyethylenes into which alkyl branches and functional groups are regularly introduced by ADMET of the branched diene compounds, followed by hydrogenation of the formed polyolefins.⁴³ These polymers have properties industrially very useful. The first example is synthesis of perfectly linear polyethylene by the exhaustive hydrogenation of polyoctenamer made by ADMET of 1,9-decadiene.⁴⁴ The linear polyethylene obtained by ADMET has melting point at 131–134 °C, while the industrially produced high-density polyethylene at 133–138 °C.⁴⁵ In addition, introduction of the substituent branching into polyethylene main chain precisely changes the melting

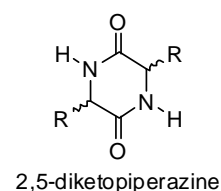


temperature and the crystallinity. Their melting temperatures (T_m) determined by DSC measurements are observed as sharper endothermic peaks than those of ethylene/propylene copolymers synthesized by chain-growth polymerization technique. Their T_m ranges and T_m values are also lower than the copolymers'.

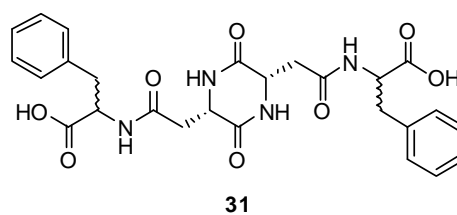
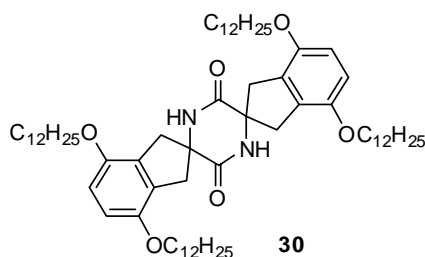
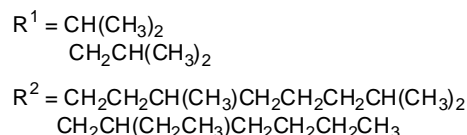
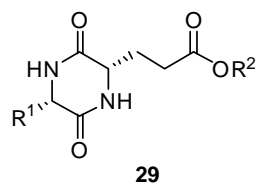
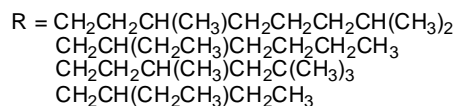
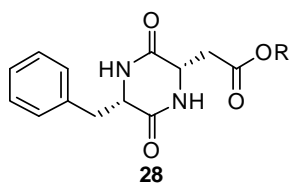


A lot of polymers have been synthesized by ADMET. ADMET has been reported as the method of not only polymer synthesis but also stabilization of supramolecule architecture and synthesis of supramolecular graft copolymers.⁴⁶

Diketopiperazine (DKP). 2,5-Diketopiperazines (DKPs), head-to-tail peptide cyclodimers, are frequently generated as unwanted byproducts or degradation products in the synthesis of oligopeptides.⁴⁷ Due to the similarity of DKPs to peptides,⁴⁸ they often exhibit a wide range of biological activities, e.g., antibiotic,⁴⁹ antifungal,⁵⁰ and anticancer⁵¹ effect. DKPs are also considered to be privileged structures for drug development.⁵² The N atom of the amide group is constrained within the DKP ring, leading to different properties from oligopeptides and lowering of conformational flexibility. Therefore, various artifices are needed for DKP synthesis and a number of DKPs have been provided by several methods.⁵³

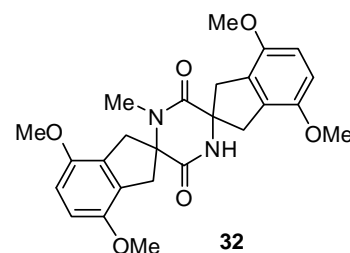


DKP has two *s-cis* amide groups in a horizontal position to the DKP ring. It is noted that DKPs align regularly in the solid state based on hydrogen bonding

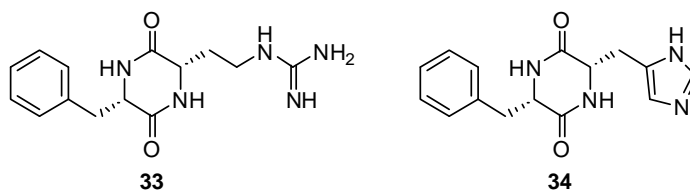


between the amide groups, and their crystal structures have been well examined.⁵⁴ Furthermore, aggregation behavior in solution is observed in a fashion similar to that in the solid state. Combination of long alkyl chains, phenyl groups, and so on (**28**, **29**) leads to the application as the gelators for oil and ionic liquid, where strong hydrogen bonding exists between the amide groups of DKP, and hydrogen bonding between the other amide groups, van der Waals interaction, and π -stacking support the interaction.⁵⁵ It has been reported that **30** aggregates three-dimensionally based on hydrophobic interaction and π -stacking of the side chains as well as hydrogen bonding between the amide groups, leading to thermotropic liquid crystallinity.⁵⁶ Basic solutions of tetrapeptide derived from L-aspartic acid diketopiperazines (**31**) are shown to form microcapsules when acidified. Intramolecular hydrogen bonding between the β -carboxy group of aspartic acid and the amide group of DKP induces the stereo configuration which has a tendency to pack properly. No similar aggregation is observed with glutamic acid analog.⁵⁷ *N*-Methylation of one amide group improves their solubility, leading to the detailed examination about the aggregation behavior in solution.⁵⁸ For example, ¹H NMR spectra of **32** can be measured in a nonpolar

solvent at variable temperatures and in various concentrations, and the dimerization constants of **32** (K_{aNH} 0.4–0.7 M⁻¹, K_{aHa} \approx 0.1 M⁻¹) are calculated from the peak shifts of protons of the amide groups and the phenyl groups. The dimer formation of **32** depends on concentration is also confirmed by ESI mass spectra.



The Strecker amino acid synthesis using DKPs has been reported by Lipton and coworkers in 1996.⁵⁹ They selected to use **33**, which is used as an asymmetric hydrocyanation catalyst of aldehydes.⁶⁰ **34** catalyzes cyanohydrin synthesis in low concentration (2 mol%) in high activity, while it does not induce the asymmetric Strecker reaction of imines.^{60a}



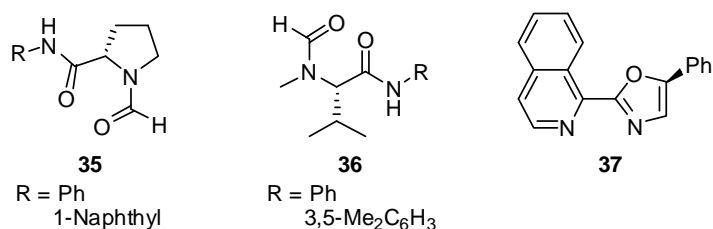
Although DKPs are very useful as described above, there have been few reports about the introduction of DKPs into polymers and cyclic peptides due to their low solubility and difficulty in DKP synthesis.⁶¹

Asymmetric Organocatalyst for Ketimines. The asymmetric reactions using organic compounds have recently attracted much attention as the Strecker synthesis using DKPs. They are called organocatalysts. They are very useful from the viewpoint of green chemistry because their lower cost and lower toxicity than metal complexes will enable large scale reactions. Easy in handling based on their stability against water and air is also the advantage.

MacMillan and coworkers have revealed in 2000 that asymmetric Diels–Alder reaction proceeds by secondary amine derivatives,⁶² and they have propounded the concept of organocatalyst. In that year, List and coworkers reported the catalytic ability of proline for aldol reaction,^{2a} which prompted many researchers to study organocatalysts.

Asymmetric reduction of ketimines using organocatalysts is one of the most important reactions among many organocatalytic reactions ever developed. Produced chiral amines, which are common intermediates in the synthesis of pharmaceutical drugs and agrochemicals, are currently synthesized by reduction of ketimines using metal complexes.⁶³ High-pressure hydrogenation⁶⁴ and hydrogen transfer⁶⁵ make handling complicated and have such problems as leaching of metal and high cost. Hydroboration, catalyzed by chiral oxazaborolidines, avoids most of these problems and shows high enantioselectivity, but remains a cost problem.⁶⁶ Inexpensive silanes are used for transition-metal-catalyzed hydrosilylation as a reduction agent, but metal leaching is unpreventable.⁶⁷ The recently developed reductions of imines, which use the Hantzsch dihydropyridine as a stoichiometric reducing agent and a chiral Brønsted acid as an organocatalyst, are also tainted by the cost implications.⁶⁸

Metal-free reaction using trichlorosilane as an alternative to those described above has been developed recently. Trichlorosilane is activated by Lewis base such as R_3N , DMF, MeCN, and so on,⁶⁹ which is applied for the reaction. Matsumura and coworkers have reported the reduction of ketimines using formamides derived from L-proline (**35**) up to 66% ee.⁷⁰ More recently, Malkov and Kočovský have



improved the enantioselectivity using **36** and **37**.⁷¹ **37** exhibits a high catalytic activity for the reduction of not only ketimines but also ketones, and gives optically active amines and alcohols with high ee. Reduction using S chiral sulfinamide has also been reported to proceed in high yields and high enantioselectivity.⁷²

Objectives of This Thesis

As demonstrated above, higher order structures of proteins are accumulated based on intra- and intermolecular noncovalent interactions such as hydrogen bonding, hydrophobic stacking, solvation, and electrostatic interaction. Combination of natural amino acids and diketopiperazines, the cyclic dimers of them, into synthetic polymers and supramolecular polymers is expected to contribute to construction of higher order structures having peptide-mimetic functionality and chirality with biodegradability and biocompatibility, which have been required for synthetic polymers. Conformational change of the polymers in response to external stimuli such as temperature, polarity of solvents, and pH leads to the creation of novel functional materials.

In this thesis, novel chiral amino acids-containing polyacetylenes and diketopiperazine-containing polycondensates are synthesized, and their chiroptical properties and their higher order structures are examined with the purpose of the expression of novel features. The author focuses attention especially on hydrogen bonding among various noncovalent interactions, and arranges the functionalities precisely through the formation of higher order structure based on hydrogen bonding.

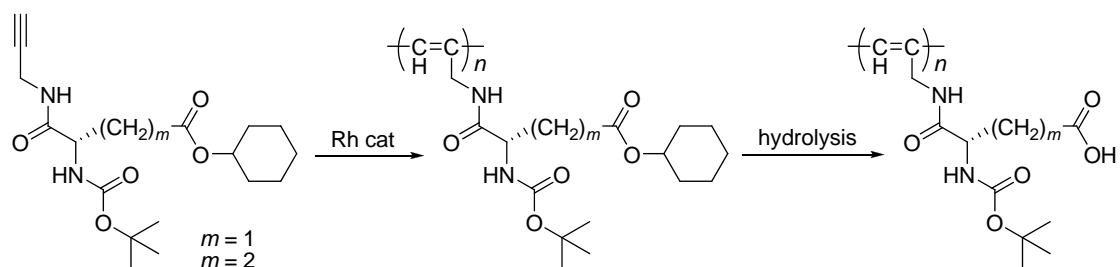
Outline of This Thesis

The present thesis consists of three parts. **Part I** (Chapters 1–3) deals with the novel helical polyacetylenes showing unique properties and applications based on

the amino acid introduced into the side chains. **Part II** (Chapters 4 and 5) focuses on the diketopiperazine-containing polymers obtained by two polycondensation methods; dehydration polycondensation and acyclic diene metathesis polycondensation. **Part III** (Chapters 6 and 7) describes the examination of the aggregation properties of diketopiperazine derivatives in detail by the modifications such as introduction of long alkyl chain and *N*-alkylation of the amide group.

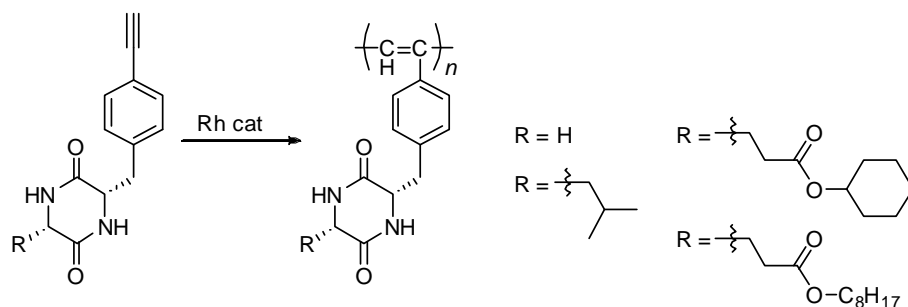
Part I describes synthesis of amino acid-derived helical polyacetylenes and their chiroptical properties based on the helical structures. Responsiveness for the external stimuli of the helical conformations and their applications as an asymmetric catalyst are examined.

Chapter 1 demonstrates polymerization of L-aspartic and L-glutamic acid-based novel *N*-propargylamides with a rhodium catalyst. The helical structures of the formed polymers and their tightness are also examined using CD and UV-vis spectra. The presence of intramolecular hydrogen bonding in stabilizing the helices is confirmed by liquid state IR spectroscopy. The polymers carrying free carboxy groups are obtained by alkaline hydrolysis of the protected polymers. It is examined how addition of KOH affects the screw sense and the tightness of the deprotected polymer derived from L-glutamic acid.

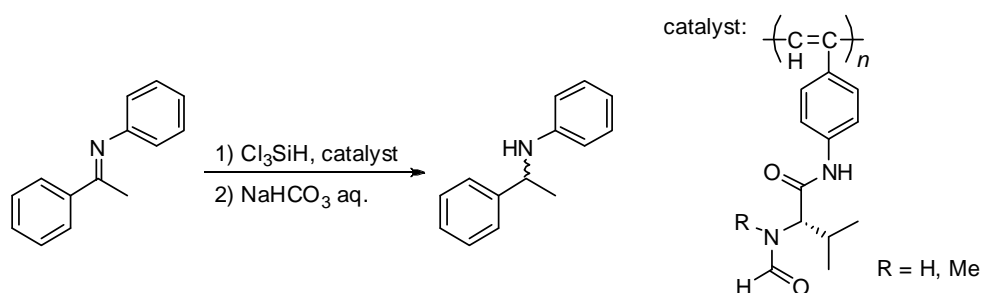


Chapter 2 concerns the synthesis of novel optically active phenylacetylenes having diketopiperazine from L-phenylalanine and the helical conformation of the formed polymers. The conformation of the polymers in DMF and in $CHCl_3$ is

studied by the CD and UV-vis spectroscopy. It is also investigated how the conformation of the polymers are influenced by addition of carboxylic acids such as trifluoroacetic acid. The most stable conformer of the polymers is calculated by molecular mechanics.



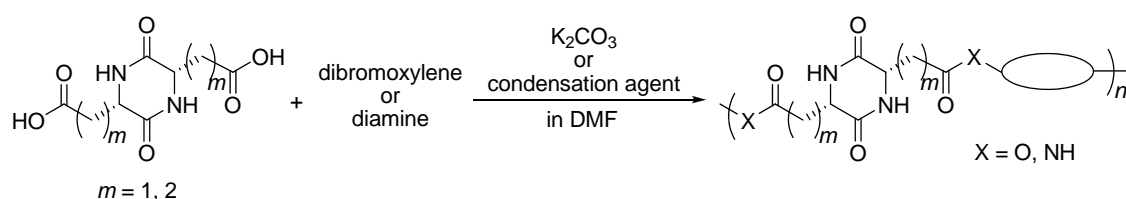
Chapter 3 deals with the study on the secondary structure of poly(phenylacetylene)s derived from valine and their catalysis for asymmetric reduction of aromatic ketimines. The helical structures of the formed polymers in various solvents are examined by CD and UV-vis spectroscopic analyses. It is investigated how the helical structures of the polymers affect the enantioselectivity of reduction of ketimines using trichlorosilane.



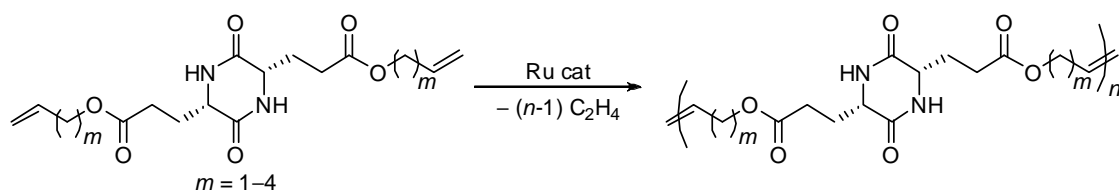
Part II deals with the synthesis of acidic amino acid-derived diketopiperazine containing polymers using polycondensation methods. Their assembling properties based on hydrogen bonding between diketopiperazine moieties are also studied.

Chapter 4 discusses the synthesis and polycondensation of aspartic and glutamic acid-based diketopiperazines, *cyclo*(L-asparaginyl-L-asparaginyl) (DKPD)

and *cyclo*(L-glutaminyl-L-glutaminyl) (DKPE). The aggregation behavior of DKPD cyclohexyl ester is determined by ^1H NMR measurements at various temperatures and in various concentrations. Polycondensation of DKPD and DKPE with α,α' -dibromoxylenes is carried out using K_2CO_3 as a base in DMF to obtain the corresponding polyesters. Further, polycondensation of DKPE with various diamines is performed using a condensation agent in DMF to obtain the corresponding polyamides.



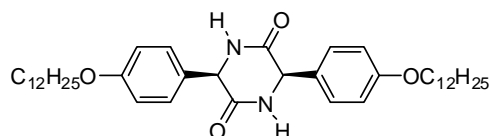
Chapter 5 delineates the acyclic diene metathesis polycondensation of L-Glutamic acid diketopiperazine ω -alkenyl esters using ruthenium catalysts. The crystalline structures of the formed polymers are mentioned using X ray diffraction measurements and differential scanning calorimetric analyses. Dynamic light scattering and differential scanning calorimetric measurements are studied for the investigation of the aggregation behavior of the polymers in *N,N*-dimethylformamide.



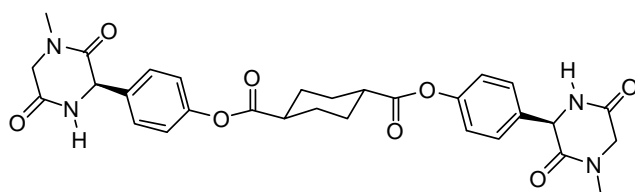
Part III describes the synthesis and the association properties of diketopiperazine derived from D-*p*-hydroxyphenylglycine.

Chapter 6 deals with the synthesis of diketopiperazine having long alkyl chains from D-*p*-hydroxyphenylglycine and their self-assembling property based on

the hydrogen bonding. It is examined whether hydrogen bonding and stacking exist or not to align the diketopiperazine molecules in solution using ^1H NMR and UV-vis spectroscopy. The possible molecular structure is also calculated by molecular mechanics calculation.



Chapter 7 demonstrates the synthesis of *N*-methylated diketopiperazine from *D*-*p*-hydroxyphenylglycine via the corresponding dipeptide. Atomic force microscope measurement of the DMSO solution is examined to observe some assembling objects of diketopiperazines.



References

- (1) (a) Clapés, P.; Infante, M. R. *Biocatal. Biotransform.* **2002**, *20*, 215. (b) Martínez, V.; Sánchez, L.; Busquets, M. A.; Infante, M. R.; Vinardell, M. P.; Mitjans, M. *Amino Acids* **2007**, *33*, 459. (c) Xia, J.; Qian, J.; Nnanna, I. A. *J. Agric. Food Chem.* **1996**, *44*, 975. (d) Marques, E. F.; Brito, R. O.; Silva, S. G.; Rodríguez-Borges, J. E.; Vale, M. L. d.; Gomes, P.; Araújo, M. J.; Söderman, O. *Langmuir* **2008**, *24*, 11009. (e) Takehara, M. *Cosmet. Toiletries* **1983**, *98*, 51. (f) Trabocchi, A.; Scarpi, D.; Guarna, A. *Amino Acids* **2008**, *34*, 1. (g) Oldfield, E. *Annu. Rev. Phys. Chem.* **2002**, *53*, 349.
- (2) (a) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Guillena, G.; Nájera, C.; Ramón, D. J. *Tetrahedron Asymmetry* **2007**, *18*, 2249. (c) Xu, L. W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047. (d) Kizmaier, U. *Angew. Chem. Int. Ed.* **2005**, *44*, 2186.
- (3) (a) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (b) Berkessel, A. *Pure Appl. Chem.* **2005**, *77*, 1277. (c) Budt, K. H.; Vatele, J. M.; Kishi, Y. *J.*

- Am. Chem. Soc.* **1986**, *108*, 6080. (d) DeGrado, W. F.; Wasserman, Z. R.; Lear, J. D. *Science* **1989**, *243*, 622.
- (4) (a) Sanda, F.; Endo, T. *Macromol. Chem. Phys.* **1999**, *200*, 2651. (b) Schlaad, H.; Antonietti, M. *Eur. Phys. J. E.* **2003**, *10*, 17. (c) Löwik, D. W. P. N.; van Hest, J. C. M. *Chem. Soc. Rev.* **2004**, *33*, 234. (d) Katsarava, R. *Macromol. Symp.* **2003**, *199*, 419.
- (5) (a) Branden, C.; Tooze, J. *Introduction to Protein Structure*, 2nd ed.; Garland Publishing: New York, 1999. (b) Voet, D.; Voet, J. G.; Prett, C. W. *Fundamentals of Biochemistry*; Wiley: New York, 1999.
- (6) (a) Hanes, C. S. *New Phytol.* **1937**, *36*, 101, 189. (b) Freudenberg, K.; Schaaf, E.; Dupert, G.; Ploetz, T. *Naturwissenschaften* **1937**, *27*, 850.
- (7) Pauling, L.; Corey, R. B.; Branson, H. R. *Proc. Natl. Acad. Sci. U.S.A.* **1951**, *378*, 205.
- (8) Watson, J. D.; Crick, F. H. C. *Nature* **1953**, *171*, 737.
- (9) Natta, G.; Pino, P.; Corradini, P.; Danusso, F.; Mantitca, E.; Nazzanti, G.; Moraglio, G. *J. Am. Chem. Soc.* **1955**, *77*, 1708.
- (10) (a) Okamoto, Y.; Suzuki, K.; Ohta, K.; Hatada, K.; Yuki, H. *J. Am. Chem. Soc.* **1979**, *101*, 4763. (b) Okamoto, Y.; Suzuki, K.; Yuki, H. *J. Polym. Sci., Polym. Chem. Ed.* **1980**, *18*, 3043. (c) Okamoto, Y.; Shohi, H.; Yuki, H. *J. Polym. Sci., Polym. Lett. Ed.* **1983**, *21*, 601. (d) Nakano, T.; Okamoto, Y.; Hatada, K. *J. Am. Chem. Soc.* **1992**, *114*, 1318. (e) Nakano, T.; Hidaka, Y.; Okamoto, Y. *Polym. J.* **1998**, *30*, 596.
- (11) (a) Vogl, O.; Miller, H. C.; Sharky, W. H. *Macromolecules* **1972**, *5*, 658. (b) Corley, L. S.; Vogl, O. *Polym. Bull.* **1980**, *3*, 211. (c) Vogl, O.; Corley, L. S.; Harris, W. J.; Jaycox, G. D.; Zhang, J. *Macromol. Chem. Suppl.* **1985**, *13*, 1. (d) Zhang, J.; Jaycox, G. D.; Vogl, O. *Polym. J.* **1987**, *19*, 603. (e) Vogl, O.; Xi, F.; Vass, F.; Ute, K.; Nishimura, T.; Hatada, K. *Macromolecules* **1989**, *22*, 4660. (f) Jaycox, G. D.; Vogl, O. *Macromol. Chem. Rapid Commun.* **1990**, *11*, 61. (g) Ute, K.; Hirose, K.; Kashimoto, H.; Nakayama, K.; Hatada, K.; Vogl, O. *Polym. J.* **1993**, *25*, 1175.
- (12) (a) Millich, F.; Baker, G. K. *Macromolecules* **1969**, *2*, 122. (b) van Beijinen, A. J. M.; Nolte, R. J. M.; Drenth, W.; Hezemans, A. M. K. *Tetrahedron* **1976**, *32*, 2017. (c) Kamer, P. C.; Nolte, R. J. M.; Drenth, W. *J. Am. Chem. Soc.* **1988**, *110*, 6828. (d) Deming, T. J.; Novak, B. M. *J. Am. Chem. Soc.* **1992**, *114*, 7926.
- (13) (a) Yuki, H.; Okamoto, Y.; Okamoto, I. *J. Am. Chem. Soc.* **1980**, *102*, 6358. (b) Okamoto, Y.; Honda, S.; Okamoto, I.; Yuki, H.; Murata, S.; Noyori, R.; Takaya, H. *J. Am. Chem. Soc.* **1981**, *103*, 6971. (c) Okamoto, Y.; Hatada, K.

- Liq. Chromatogr.* **1986**, 9, 369. (d) Okamoto, Y. *CHEMTECH* **1987**, 144. (e) Nakano, T. *Liq. Chromatogr., A* **2001**, 906, 205.
- (14) Hoshikawa, N.; Hotta, Y.; Okamoto, Y. *J. Am. Chem. Soc.* **2003**, 125, 12380.
- (15) (a) Hatada, K.; Shimizu, S.-I.; Yuki, H.; Harris, W.; Vogl, O. *Polym. Bull.* **1981**, 4, 179. (b) Hatada, K.; Kitayama, T.; Shimizu, S.-I.; Yuki, H.; Harris, W.; Vogl, O. *J. Chromatogr.* **1982**, 248, 63. (c) Ute, K.; Hirose, K.; Hatada, K.; Vogl, O. *Polym. Preor. Jpn.* **1992**, 41, 1358.
- (16) (a) Takei, F.; Onitsuka, K.; Kobayashi, N.; Takahashi, S. *Chem. Lett.* **2000**, 914. (b) Takei, F.; Hayashi, H.; Onitsuka, K.; Kobayashi, N.; Takahashi, S. *Angew. Chem., Int. Ed.* **2001**, 40, 4092. (c) Takei, F.; Nakamura, S.; Onitsuka, K.; Ishida, A.; Tojo, T.; Majima, T.; Kobayashi, N.; Takahashi, S. *Chem. Lett.* **2003**, 32, 506. (d) Fujitsuka, M.; Okada, A.; Tojo, T.; Takei, F.; Onitsuka, K.; Takahashi, S.; Majima, T. *Polym. Sci., Part B* **2004**, 108, 11935.
- (17) Hida, N.; Takei, F.; Onitsuka, K.; Shiga, S.; Asaoka, T.; Takahashi, S. *Angew. Chem., Int. Ed.* **2003**, 42, 4349.
- (18) (a) Kauranen, M.; Verbiest, T.; Boutton, C.; Teerenstra, M. N.; Clays, K.; Schouten, A. J.; Nolte, R. J. M.; Persoons, A. *Science* **1995**, 270, 966. (b) Hida, N.; Takei, F.; Onitsuka, K.; Shiga, S.; Asaoka, T.; Takahashi, S. *Angew. Chem., Int. Ed.* **2003**, 42, 4349.
- (19) (a) Goodman, M.; Chen, S.-C. *Macromolecules* **1970**, 3, 398. (b) Goodman, M.; Chen, S.-C. *Macromolecules* **1971**, 4, 625.
- (20) (a) Green, M. M.; Gross, R. A.; Crosby, C., III; Schilling, R. C. *Macromolecules* **1987**, 20, 992. (b) Green, M. M.; Andreola, C.; Munoz, B.; Reidy, M. P.; Zero, K. *J. Am. Chem. Soc.* **1988**, 110, 4063. (c) Green, M. M.; Peterson, N. C.; Sato, T.; Teramoto, A.; Cook, R.; Lifson, S. *Science* **1995**, 268, 1860.
- (21) Cheon, K. S.; Selinger, J. V.; Green, M. M. *Angew. Chem., Int. Ed.* **2000**, 39, 1482.
- (22) Green, M. M.; Garetz, B. A.; Munoz, B.; Chang, H.; Hoke, S.; Cooks, R. G. *J. Am. Chem. Soc.* **1995**, 117, 4181.
- (23) (a) Matyjaszewski, K. *J. Inorg. Organomet.* **1992**, 2, 5. (b) Frey, H.; Möller, M.; Matyjaszewski, K. *Macromolecules* **1994**, 27, 1814. (c) Fujiki, M. *J. Am. Chem. Soc.* **1994**, 116, 6017. (d) Fujiki, M. *J. Am. Chem. Soc.* **1994**, 116, 11976. (e) Fujiki, M. *J. Am. Chem. Soc.* **1996**, 118, 7424. (f) Fujiki, M. *J. Am. Chem. Soc.* **2000**, 122, 3336. (g) Fujiki, M.; Koe, J. R.; Motonaga, M.; Nakashima, H.; Terao, K.; Teramoto, A. *J. Am. Chem. Soc.* **2001**, 123, 6253. (h) Teramoto, A.; Terao, K.; Terao, Y.; Nakamura, N.; Sato, T.; Fujiki, M. *J. Am. Chem. Soc.* **2001**, 123, 12303. (i) Fujiki, M.; Koe, J. R.; Motonaga, M.;

- Nakashima, H.; Terao, K.; Teramoto, A. *Silicon Chemistry* **2002**, *1*, 67.
- (24) Drake, A. F.; Udvarhelyi, P.; Ando, D. J.; Bloor, D.; Obhi, J. S.; Mann, S. *Polymer* **1989**, *30*, 1063.
- (25) Fiesel, R.; Halkyard, C. E.; Rampey, M. E.; Kloppenburg, L.; Studer-Martinez, S. L.; Scherf, U.; Bunz, U. H. F. *Macromol. Rapid Commun.* **1999**, *20*, 107.
- (26) (a) Bouman, M. M.; Havinga, E. E.; Jannsenn, R. A. J.; Meijer, E. W. *Mol. Cryst. Liq. Cryst.* **1994**, *256*, 439. (b) Langeveld-Voss, B. M. W.; Chrietaans, M. P. T.; Jannsenn, R. A. J.; Meijer, E. W. *Macromolecules* **1998**, *31*, 6702.
- (27) Pu, L. *Acta Polym.* **1997**, *48*, 116.
- (28) Masuda, T.; Sanda, F. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, **2003**, *3*, 375.
- (29) (a) Shirakawa, H.; Masuda, T.; Takeda, K. "The Chemistry of Triple-Bonded Functional Groups", Supplement C2, Patai, S. ed., **2**, Wiley, Chichester **1994**, Chapter 17. (b) Masuda, T. "Catalyst in Precision Polymerization", Kobayashi, S. ed Wiley, Chichester **1997**, Chapter 2.4. (c) Masuda, T. "Polymeric Material Encyclopedia", Salamone, J. C. ed., **1**, CRC Press, Boca Raton, FL **1996**, 32.
- (30) Ciardelli, F.; Lanzillo, S.; Pieroni, O. *Macromolecules* **1974**, *7*, 174.
- (31) Moore, J. S.; Gorman, C. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1991**, *113*, 1704.
- (32) (a) Aoki, T.; Kokai, M.; Shinohara, K.; Oikawa, E. *Chem. Lett.* **1993**, 2009. (b) Yashima, E.; Matsushima, T.; Nomura, T.; Okamoto, Y. *Korea Polym. J.* **1996**, *4*, 139. (c) Aoki, T.; Shinohara, K.-I.; Kaneko, T.; Oikawa, E. *Macromolecules* **1996**, *29*, 4192. (d) Aoki, T.; Kaneko, T.; Maruyama, N.; Sumi, A.; Takahashi, M.; Sato, T.; Teraguchi, M. *J. Am. Chem. Soc.* **2003**, *125*, 6346.
- (33) (a) Yashima, E.; Huang, S.; Okamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1811. (b) Yashima, E.; Huang, S.; Matsushima, T.; Okamoto, Y. *Macromolecules* **1995**, *28*, 4184. (c) Yashima, E.; Matsushima, T.; Okamoto, Y. *J. Am. Chem. Soc.* **1995**, *117*, 11596. (d) Yashima, E.; Maeda, K.; Okamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9800. (e) Yashima, E.; Nimura, T.; Matsushima, T.; Okamoto, Y. *Chem. Lett.* **1996**, 955. (f) Yashima, E.; Matsushima, T.; Okamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 6345. (g) Saito, M. A.; Maeda, K.; Onouchi, K.; Yashima, E. *Macromolecules* **2000**, *33*, 4616. (h) Yashima, E.; Maeda, K.; Onouchi, K. *Nature* **1999**, *399*, 449. (i) Nonokawa, R.; Oobo, M.; Yashima, E. *Macromolecule.* **2003**, *36*, 6599. (j) Nonokawa, R. and Yashima, E. *J. Am. Chem. Soc.* **2003**, *125*, 1278.
- (34) (a) Nakako, H.; Nomura, R.; Tabata, M.; Masuda, T. *Macromolecules* **1999**,

- 32, 2861. (b) Nakako, H.; Mayahara, Y.; Nomura, R.; Tabata, M.; Masuda, T. *Macromolecules* **2000**, *33*, 3978. (c) Nomura, R.; Fukishima, Y.; Nakako, H.; Masuda, T. *J. Am. Chem. Soc.* **2000**, *122*, 8830. (d) Nakako, H.; Nomura, R.; Masuda, T. *Macromolecules* **2001**, *34*, 1496.
- (35) (a) Nomura, R.; Tabei, J.; Masuda, T. *J. Am. Chem. Soc.* **2001**, *123*, 8430. (b) Tabei, J.; Nomura, R.; Masuda, T. *Macromolecules* **2002**, *35*, 2955. (c) Tabei, J.; Nomura, R.; Masuda, T. *Macromolecules* **2002**, *35*, 5405. (d) Tabei, J.; Nomura, R.; Sanda, F.; Masuda, T. *Macromolecules* **2003**, *36*, 8603. (e) Tabei, J.; Shiotsuki, M.; Sanda, F.; Masuda, T. *Macromolecules*, **2005**, *38*, 9448. (f) Gao, G.; Sanda, F.; Masuda, T. *Macromolecules*, **2003**, *36*, 3938.
- (36) (a) Nomura, R.; Nishiura, S.; Tabei, J.; Sanda, F.; Masuda, T. *Macromolecules* **2003**, *36*, 5076. (b) Sanda, F.; Nishiura, S.; Shiotsuki, M.; Masuda, T. *Macromolecules* **2005**, *38*, 3075.
- (37) Sanda, F.; Araki, H.; Masuda, T. *Macromolecules* **2005**, *38*, 10605.
- (38) (a) Aoki, T.; Kobayashi, Y.; Kaneko, T.; Oikawa, E.; Yamamura, Y.; Fujita, Y.; Teraguchi, M.; Nomura, T.; Masuda, *Macromolecules*, **1999**, *32*, 79. (b) Lam, J. W. Y.; Dong, Y. P.; Cheuk, K. K. L.; Law, C. C. W.; Lai, L. M.; Tang, B. Z. *Macromolecules* **2004**, *37*, 6695.
- (39) (a) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*; John Wiley & Sons: New York, **1994**, 280. (b) Schaverien, C. J.; Dewan, J. C.; Schrock, R. R. *J. Am. Chem. Soc.* **1986**, *108*, 2771. (c) Schrock, R. R.; DePue, R. T.; Feldman, J.; Schaverien, C. J.; Dewan, J. C.; Liu, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 1423. (d) Schrock, R. R.; DePue, R. T.; Feldman, J.; Yap, K. B.; Yang, D. C.; Davis, W. M.; Park, L.; DiMare, M.; Schofield, M.; Anhaus, J.; Walborsky, E.; Evit, E.; Krüger, C.; Betz, P. *Organometallics* **1990**, *9*, 2262. (e) Murdzek, J. S.; Schrock, R. R. *Organometallics* **1987**, *6*, 1373. (f) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. J. *Am. Chem. Soc.* **1990**, *112*, 3875.
- (40) (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974. (b) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858. (c) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. (d) Wu, Z.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503. (e) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (f) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2490. (g) Bielawski, C. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2000**, *37*, 2903. (h) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

- (41) (a) Wagener, K. B.; Boncella, J. M.; Nel, J. G.; Konzelman, J. *Macromolecules* **1990**, *23*, 5155. (b) Wagener, K. B.; Boncella, J. M.; Nel, J. G. *Macromolecules* **1991**, *24*, 1649. (c) Wagener, K. B.; Puts, R. D.; Smith, D. W. Jr. *Makromol. Chem. Rapid. Comm.* **1991**, *12*, 419. (d) Wagener, K. B.; Smith, D. W. *Macromolecules* **1991**, *24*, 6073. (e) Wagener, K. B.; Smith, D. W. *Macromolecules* **1993**, *26*, 1633.
- (42) (a) Wagener, K. B.; Boncella, J. M.; Nel, J. G. *Macromolecules* **1991**, *24*, 2649. (b) Wagener, K. B.; Brzezinska, K. R. *Macromolecules* **1991**, *24*, 5273. (c) Wagener, K. B.; Patton, J. T. *Macromolecules* **1993**, *26*, 249. (d) Portmess, J. D.; Wagener, K. B. *J. Polym. Sci. Polym. Chem.* **1996**, *34*, 1353. (e) Wolfe, P. S.; Wagener, K. B. *Macromol. Rapid. Commun.* **1998**, *19*, 305. (f) Wolfe, P. S.; Wagener, K. B. *Macromolecules* **1999**, *32*, 7961. (g) Brzezinska, K. R.; Schitter, R.; Wagener, K. B. *J. Polym. Sci. Polym. Chem.* **2000**, *38*, 1544. (h) Cummings, S. K.; Smith, D. W.; Wagener, K. B. *Macromol. Rapid. Commun.* **1995**, *16*, 347.
- (43) (a) Smith, J. A.; Brzezinska, K. R.; Valenti, D. J.; Wagener, K. B. *Macromolecules* **2000**, *33*, 3781. (b) Watson, M. D.; Wagener, K. B. *Macromolecules* **2000**, *33*, 8963. (c) Watson, M. D.; Wagener, K. B. *Macromolecules* **2000**, *33*, 5411. (d) Watson, M. D.; Wagener, K. B. *Macromolecules* **2000**, *33*, 3196.
- (44) (a) Ogara, J. E.; Wagener, K. B. *Makromolekulare Chemie Rapid Communication* **1993**, *14*, 657.
- (45) (a) Hoffman, J. D. *Polymer* **1982**, *23*, 656-670. (b) Hoffman, J. D. *Polymer* **1983**, *24*, 3.
- (46) (a) Jin, W.; Fukushima, T.; Kosaka, A.; Niki, M.; Ishii, N.; Aida, T. *J. Am. Chem. Soc.* **2005**, *127*, 8284. (b) Ohkawa, H.; Ligthart, G. B. W. L.; Sijbesma, R. P.; Meijer, E. W. *Macromolecules* **2007**, *40*, 1453.
- (47) (a) Wei, Y; Pei, D. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1073. (b) Barany, G.; Albericio, F. *J. Am. Chem. Soc.* **1985**, *107*, 4936. (c) Anne, C.; Fournié, Zaluski, M. C.; Roques, B. P.; Cornille, F. *Tetrahedron Lett.* **1998**, *39*, 8973.
- (48) Witiak, D. T.; Wei, Y. *Prog. Drug. Res.* **1990**, *35*, 249.
- (49) Rameshkumar, N.; Ashokkumar, M.; Subramanian, E. H.; Ilavarasan, R.; Sridhar, S. K. *Eur. J. Med. Chem.* **2003**, *38*, 1001.
- (50) McClelland, K.; Milne, P. J.; Lucieto, F. R.; Frost, C.; Brauns, S. C.; van de Venter, M.; Du, Plessis, J.; Dyason, K. *J. Pharm. Pharmacol.* **2004**, *56*, 1143.
- (51) Kanoh, K.; Kohno, S.; Asari, T.; Harada, T.; Kataba, J.; Muramatsu, M.; Kawashima, H.; Sekiya, H.; Uno, I. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2847.

- (52) Horton, D. A.; Boume, G. T.; Smythe, M. L. *Mol. Diversity* **2002**, *5*, 289.
- (53) (a) Carlson, K. L.; Lowe, S. L.; Hoffmann, M. R.; Thomasson, K. A. *J. Phys. Chem. A* **2005**, *109*, 5463. (b) Parrish, D. A.; Mathias, L. J. *J. Org. Chem.* **2002**, *67*, 1820. (c) Rodionov, I. L.; Rodionova, L. N.; Baidakova, L. K.; Romashko, A. M.; Balashova, T. A.; Ivanov, V. T. *Tetrahedron* **2002**, *58*, 8515. (d) Hulme, C.; Morrisette, M. M.; Volz, F. A.; Burns, C. J. *Tetrahedron* **1998**, *39*, 1113. (e) Tullberg, M.; Grøtli, M.; Luthman, K. *Tetrahedron* **2006**, *62*, 1. (f) Stark, T.; Hofmann, T. *J. Agric. Food Chem.* **2005**, *53*, 7222.
- (54) (a) Du, Y.; Creighton, C. J.; Tounge, B. A.; Reitz, A. B. *Org. Lett.* **2004**, *6*, 309. (b) Lyssenko, K. A.; Lenev, D. A.; Kostyanovsky, R. G. *Tetrahedron* **2002**, *58*, 8525. (c) Palacin, S.; Chin, D. N.; Simanek, E. E.; MacDonald, J. C.; Whitesides, G. M.; McBride, M. T.; Palmore, G. T. R. *J. Am. Chem. Soc.* **1997**, *119*, 11807. (d) Chin, D. N.; Palmore, T. R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 2115. (e) Jagadosh, B.; Carducci, M. D.; Bosshard, C.; Günter, P.; Margolis, J. I.; Williams, L. J.; Mash, E. A. *Cryst. Growth Des.* **2003**, *3*, 811.
- (55) (a) Yang, Y.; Suzuki, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Chem. Commun.* **2004**, 1332. (b) Hanabusa, K.; Mastumoto, M.; Kimura, M.; Kakehi, A.; Shirai, H. *J. Colloid Interface Sci.* **2000**, *224*, 231. (c) Hanabusa, K.; Fukui, H.; Suzuki, M.; Shirai, H. *Langmuir* **2005**, *21*, 10383.
- (56) Kloster, R. A.; Carducci, M. D.; Mash, E. A. *Org. Lett.* **2003**, *5*, 3683.
- (57) Bergeron, R. J.; Phanstiel IV, O.; Yao, G. W.; Milstein, S.; Weimar, W. R. *J. Am. Chem. Soc.* **1994**, *116*, 8479.
- (58) Kloster, R. A.; Selby, H. D.; Miller, W. B. III; Mash, E. A. *J. Org. Chem.* **2005**, *70*, 8693.
- (59) (a) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910. (b) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *Amino Acids* **1996**, *11*, 259. (c) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795. (d) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481.
- (60) (a) Oku, J.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1981**, 229. (b) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181. (c) Danda, H.; Nishikawa, H.; Otaka, K. *J. Org. Chem.* **1991**, *56*, 6740. (d) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649.
- (61) (a) Majó, M. A.; Bou, J. J.; Herranz, C.; Muñoz-Guerra, S. *Macromol. Chem. Phys.* **2006**, *207*, 615. (b) Akerlund, J.; Harmeier, S.; Pumphrey, J.; Timm, D. C.; Brand, J. I. *J. Appl. Polym. Sci.* **2000**, *78*, 2213. (c) Kunisaki, T.; Kawai, K.; Hirohata, K.; Minami, K.; Kondo, K. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 927.

- (62) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.
- (63) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis Vol. I-III*. Springer, Heidelberg, **1999**.
- (64) (a) Xial, D.; Zhang, X. *Angew. Chem. Int. Ed.* **2001**, *40*, 3425. (b) Jiang, X. B.; Minnaard, A. J.; Hessen, B.; Feringa, B. L.; Duchateau, A. L. L.; Andrien, J. G. O.; Boogers, J. A. F.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 1503. (c) Cobley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, *345*, 195. (d) Okuda, J. Verch, S.; Stürmer, R.; Spaniol, T. S. *J. Organomet. Chem.* **2000**, *605*, 55. (e) Samec, J. S. M.; Bäckvall, J. E. *Chem. Eur. J.* **2002**, *8*, 2955.
- (65) (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.
- (66) (a) Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395. (b) Cho, B. T.; Chun, Y. S. *J. Chem. Soc., Perkin. Trans. 1* **1990**, 3200. (b) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1992**, *3*, 1583.
- (67) (a) Riant, O.; Mostefai, N.; Courmarcel, J. *Synthesis* **2004**, 2943. (b) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779. (c) Reding, M. T.; Buchwald, S. L. *J. Org. Chem.* **1998**, *63*, 6344. (d) Verdaguer, X.; Lange, U. E. W.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1998**, *37*, 1103. (e) Vedejs, E.; Trapencieris, P.; Suna, E. *J. Org. Chem.* **1999**, *64*, 6724. (f) Hansen, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 713. (g) Nishikori, H.; Yoshihara, R.; Hosomi, A. *Synlett* **2003**, 561. (h) Lipshutz, B. H.; Shimizu, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 2228.
- (68) (a) Ingh, S.; Batra, U. K. *Indian J. Chem.* **1989**, *27*, 1. (b) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (c) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424.
- (69) (a) Malkow, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. *Org. Lett.* **2002**, *4*, 1047. (b) Malkow, A. V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 9659. (c) Malkow, A. V.; Bell, M.; Vassieu, M.; Bugatti, V.; Kočovský, P. *J. Mol. Catal. A* **2003**, *196*, 179. (d) Malkow, A. V.; Dufková, L.; Farrugia, L.; Kočovský, P. *Angew. Chem.* **2003**, *115*, 3802. (e) Malkow, A. V.; Bell, M.; Castelluzzo, F.; Bugatti, V.; Kočovský, P. *Org. Lett.* **2005**, *7*, 3219.
- (70) (a) Iwasaki, F.; Onomura, O.; Mishima, K.; Kanematsu, T.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2001**, *42*, 2525. (b) Iwasaki, F.; Onomura, O.; Mishima, K.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **1999**, *40*, 7507.

- (71) (a) Malkov, A. V.; Mariani, A.; MacDougall, K. N.; Kočovský, P. *Org. Lett.* **2004**, 6, 2253. (b) Malkov, A. V.; Liddon, A.; Ramirez-Lopez, P.; Bendova, L.; Haigh, D.; Kočovský, P. *Angew. Chem., Int. Ed.* **2006**, 45, 1432.
- (72) (a) Pei, D.; Wang, Z.; Wei, S.; Zhang, Y.; Sun, J. *Org. Lett.* **2006**, 8, 5913. (b) Pei, D.; Zhang, Y.; Wei, S.; Wang, M.; Sun, J. *Adv. Synth. Catal.* **2008**, 350, 619.

Part I

Synthesis and Properties of Amino Acid-derived Helical Polyacetylenes

Chapter 1

Synthesis, Chiroptical Properties, and pH-Responsiveness of Aspartic Acid- and Glutamic Acid-based Helical Polyacetylenes

Abstract

L-Aspartic and L-glutamic acid-based novel *N*-propargylamides, (*S*)-HC≡CCH₂NHCOCH(CH₂COOcyclohexyl)NHCOO*t*-Bu (**1**) and (*S*)-HC≡CCH₂NHCOCH(CH₂CH₂COOcyclohexyl)NHCOO*t*-Bu were synthesized and polymerized using a rhodium catalyst. The corresponding polymers [poly(**1**) and poly(**2**)] with moderate molecular weights were obtained in good yields. CD and UV-vis spectroscopic analyses revealed that poly(**1**) and poly(**2**) took helical structures, whose tightness was different. The presence of intramolecular hydrogen bonding was confirmed by liquid state IR spectroscopy. Poly(**1a**) and poly(**2a**) carrying free carboxyl groups were obtained by alkaline hydrolysis of poly(**1**) and poly(**2**). Poly(**1a**) did not form a helix, while poly(**2a**) formed a helix undergoing inversion of helical sense and change of tightness upon addition of KOH.

Introduction

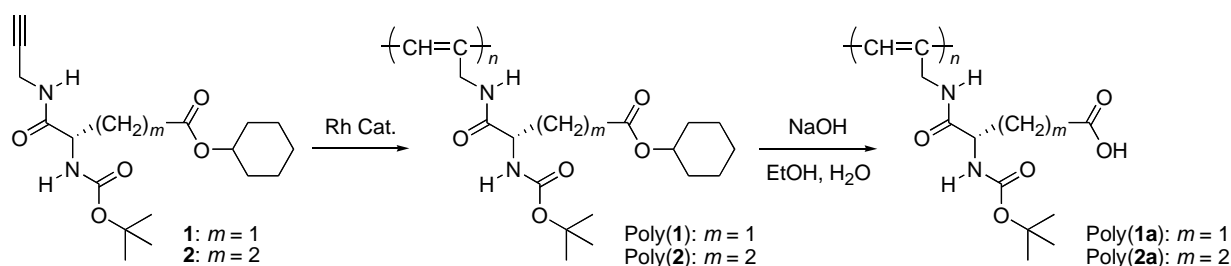
Stimuli-responsive polymers attract attention in a wide variety of fields including, pharmacy, life sciences, agriculture, and chemical engineering. Heat, light, and change of medium conditions including polarity and pH are commonly employed as stimuli, since these stimuli are easily controllable and applicable to practical usage. For instance, polymers carrying carboxyl groups such as poly(acrylic acid) and poly(methacrylic acid) have been extensively investigated as pH-responsive materials.¹ The pendent carboxyl groups accept protons at low pH, and release them at high pH. They change the conformation and molecule size drastically according to pH due to the change of electrostatic repulsion between the side chains. Helical peptides containing aspartic and/or glutamic acids undergo helix-coil transition depending on pH.² The conformation of these peptides is decided by both the stabilization effect based on hydrogen bonding between the amide groups and the state of electrostatic repulsion between the carboxyl groups.

Masuda and coworkers have recently reported the synthesis of several amino acid-carrying polyacetylenes with well-defined higher order structures. For example, an alanine-derived poly(*N*-propargylamide) takes a helical conformation in chloroform.³ Hydrogen bonding involving N–H linkage plays an important role in stabilizing the helical conformation. Serine- and threonine-derived poly(*N*-propargylamides) also form a helix, which is tight compared to alanine-derived one.⁴ This is due to the presence of hydroxyl groups that participate in the hydrogen-bonding strands between the amide groups, resulting in change of torsional angles of the polyacetylene main chain.

If the author employs aspartic or glutamic acid as a component of poly(*N*-propargylamides), it is expected to obtain a polymer undergoing helix-coil transition caused by competition between hydrogen bonding and electrostatic

repulsion in a manner similar to some peptides. The present chapter deals with synthesis of aspartic and glutamic acid-derived novel poly(*N*-propargylamides) (Scheme 1), chiroptical properties of the polymers, hydrolysis of the ester parts, and change of the chiroptical properties of the hydrolyzed polymers with pH.

Scheme 1



Results and Discussion

Synthesis and Chiroptical Properties of Poly(1) and Poly(2). Table 1 summarizes the conditions and results of the polymerization of aspartic and glutamic acid-based acetylene monomers **1** and **2** catalyzed with $(nbd)Rh^+[\eta^6-C_6H_5B^-(C_6H_5)_3]$ in THF (Scheme 1). The corresponding polymers, poly(**1**) and poly(**2**), with M_n 's of 9 600 and 24 900 were obtained in nearly quantitative yields. The specific rotations of the polymers were -35° and -813° , respectively.

The structures of poly(**1**) and poly(**2**) were examined by 1H NMR spectroscopy. It has been reported that the Rh zwitterion complex efficiently catalyzes the polymerization of monosubstituted acetylenes by the insertion mechanism to give *cis*-transoidal polyacetylenes.⁵ In the present study, the *cis* content could not be decided from the integration ratio of the *cis*-olefinic proton signal around 5 ppm, because it appeared very broadly. Since several poly(*N*-propargylamides) obtained by the polymerization using the Rh catalyst are

confirmed to have *cis* structure,⁶ it is assumed that the steric structure of poly(**1**) and poly(**2**) is also the case.

Table 1. Polymerization of **1 and **2** ^a**

monomer	yield ^b (%)	M_n^c	M_w/M_n^c	$[\alpha]_D^d$ (°)
1	91	9 600	1.71	−35
2	95	24 900	2.05	−813

^a Catalyst: (nbd)Rh⁺[η^6 -C₆H₅B[−](C₆H₅)₃], in THF, 30 °C, 1 h, [M]₀ = 0.20 M, [M]₀/[Cat] = 50. ^b Hexane-insoluble part. ^c Determined by GPC calibrated by polystyrene standards. Eluent: THF. ^d Measured by polarimetry at room temperature, *c* = 0.097–0.102 g/dL, in THF. $[\alpha]_D$ of monomers, **1**: −17°, **2**: −15°.

Figure 1 depicts the CD and UV-vis spectra of poly(**1**) and poly(**2**), along with those of poly(**1a**) and poly(**2a**) that will be described later. Poly(**1**) exhibited a clear CD signal around 260 nm based on the conjugated polyacetylene main chain. The wavelength was as much as 120–140 nm short compared to common poly(*N*-propargylamides) reported so far.⁷ It is likely that poly(**1**) forms a helix with a small pitch/diameter ratio compared to that of poly(*N*-propargylamides).⁸ On the other hand, poly(**2**) exhibited a CD signal at 400 nm, where common helical poly(*N*-propargylamides) show the signals.

It is assumed that the drastic difference of CD spectroscopic patterns between the aspartic acid- and glutamic acid-based poly(**1**) and poly(**2**) is brought about by the difference of orientation of the ester groups in the side chains. Due to even and odd methylene chains between the chiral centers and ester moieties, the ester carbonyl groups of poly(**1**) and poly(**2**) should be positioned in the opposite direction.

Consequently, the ester parts of the polymers play a role very differently to decide the polymer conformation. In fact, poly(β -benzyl L-aspartate) and poly(γ -benzyl L-glutamate) show very different conformations. The former can change the structure from right-handed α -helix, left-handed α -helix, left-handed ω -helix, and then β -sheet upon heating.⁹ On the other hand, the latter can only take right-handed α -helix as a stable conformation.¹⁰

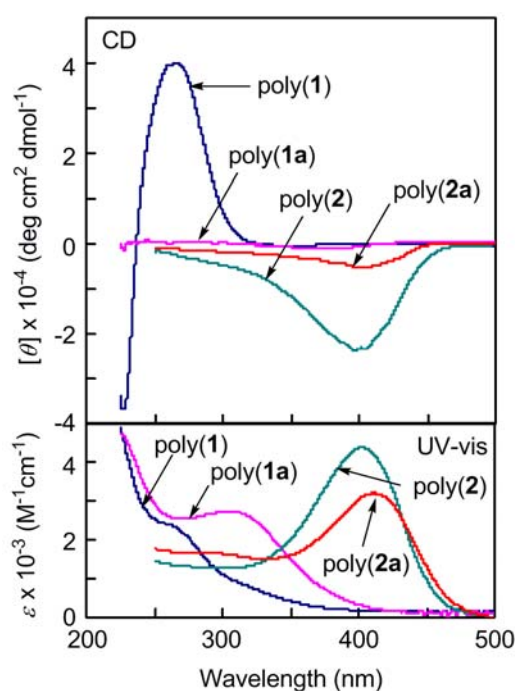


Figure 1. CD and UV-vis spectra of poly(**1**) and, poly(**2**), poly(**1a**), and poly(**2a**) measured in THF ($c = 0.5$ mM) at 0 °C.

Liquid state IR spectroscopic study was carried out to obtain information on hydrogen bonding. Figure 2 depicts the partial IR spectra of **1**, **2**, poly(**1**), and poly(**2**) measured in THF. The peaks of C=O stretching of the amide and carbamate moieties of poly(**1**) were observed at 37 and 38 cm^{-1} lower wavenumbers than those of **1**. In a similar fashion, those of poly(**2**) were 41 and 9 cm^{-1} lower than those of **2**.

These results indicate that the amide and carbamate moieties form hydrogen bonding, and it is *intramolecular* one judging from the low reagent concentration (50 mM).

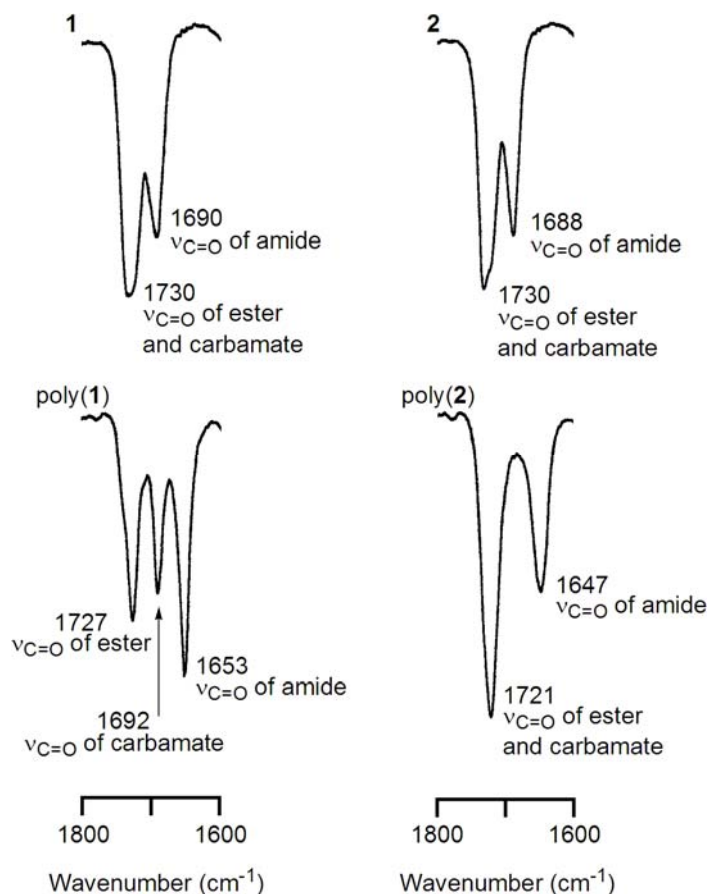


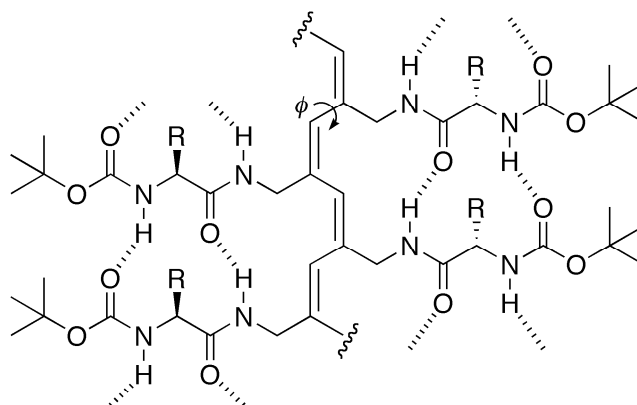
Figure 2. IR spectra of **1**, **2**, poly(**1**), and poly(**2**) measured in THF at a concentration of 50 mM.

From the results of the liquid state IR spectroscopic study, it is necessary to consider a molecular geometry accompanying intramolecular hydrogen bonding. Two ways of intramolecular hydrogen bonding are possible as shown in Chart 1. One is the hydrogen bonding formed between the amide-amide and carbamate-carbamate moieties at n th and $(n+2)$ th units (pattern [A]), and another one is formed at n th and $(n+3)$ th units (pattern [B]). The dihedral angle ϕ at the single bond in the main chain possibly ranges from 100° to 160°, and from 50° to 110° in the

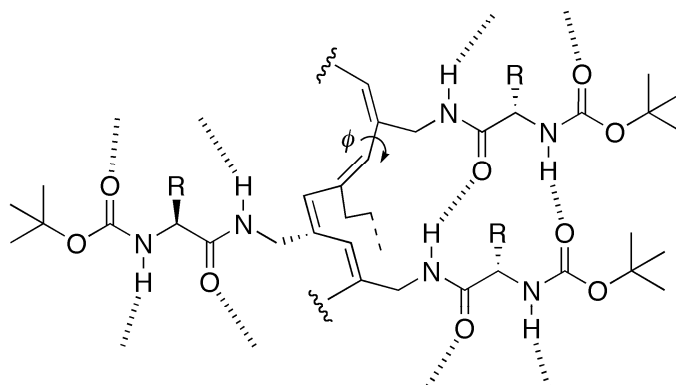
former and latter cases, respectively. The conformers out of these ranges cannot form sequential hydrogen-bonding strands, because the amide-amide and carbamate-carbamate distances become too long. Molecular mechanics calculation¹¹ suggested that the most stable conformer of poly(**1**) is the one with $\phi = 70^\circ$, which accompanies hydrogen-bonding strands formed between n th and $(n+3)$ th units. On the other hand, it was suggested that the conformer with $\phi = 140^\circ$ is the most stable in the case of poly(**2**), which forms hydrogen bonding between n th and $(n+2)$ th units (Figure 3).

Chart 1

[A] Hydrogen Bonding between n th and $(n+2)$ th Units



[B] Hydrogen Bonding between n th and $(n+3)$ th Units



R = CH₂CO₂cyclohexyl, CH₂CH₂CO₂cyclohexyl

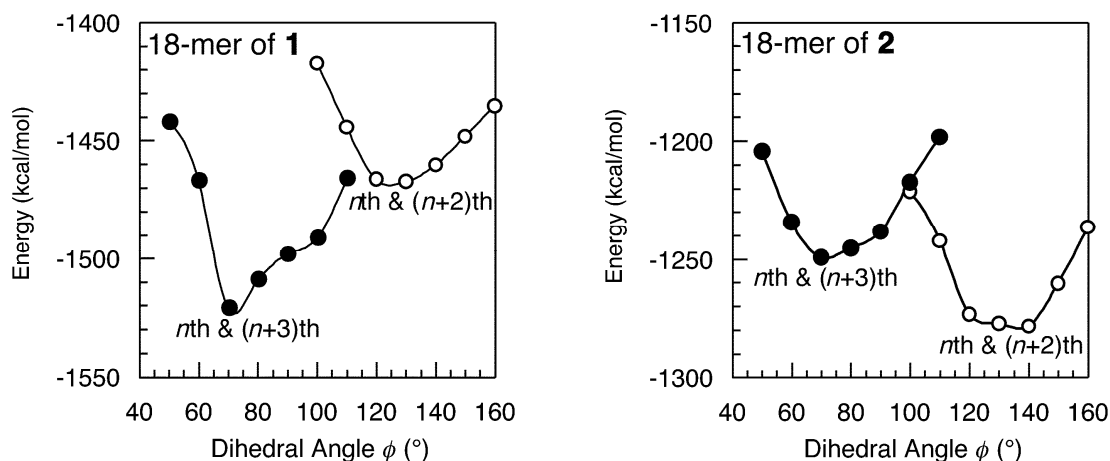


Figure 3. Relationships between the dihedral angle ϕ at the single bond in the main chain of 18-mers of **1** and **2**, and the energy calculated by MMFF94.

Hydrolysis of the Ester Groups of Poly(1) and Poly(2). Alkaline hydrolysis of the ester groups of poly(**1**) and poly(**2**) was carried out to obtain the corresponding polymers with carboxyl groups, poly(**1a**) and poly(**2a**). At first, the author attempted to obtain these polymers directly by the polymerization of the monomers with carboxyl groups, **1a** and **2a**, which were synthesized by hydrolysis of **1** and **2**. Unfortunately, however, no polymerization took place in spite of the addition of NaOH or triethylamine, unlike the case of the polymerization of 4-ethynylbenzoic acid.¹² Therefore the author abandoned the method, and employed polymer reaction to obtain the polymers with carboxyl groups. Figure 4 depicts the partial ¹H NMR spectra of poly(**2**) and poly(**2a**).¹³ The hydrolysis of the cyclohexyl ester was confirmed by the disappearance of signals *e* and *f*, which was evident from the integration ratio between the residual methylene proton signals *a*, *c*, and *d*. In a similar manner, the hydrolysis of the ester part of poly(**1**) was also confirmed. The alkaline hydrolysis of poly(**1**) and poly(**2**) successfully proceeded to give poly(**1a**) and poly(**2a**).

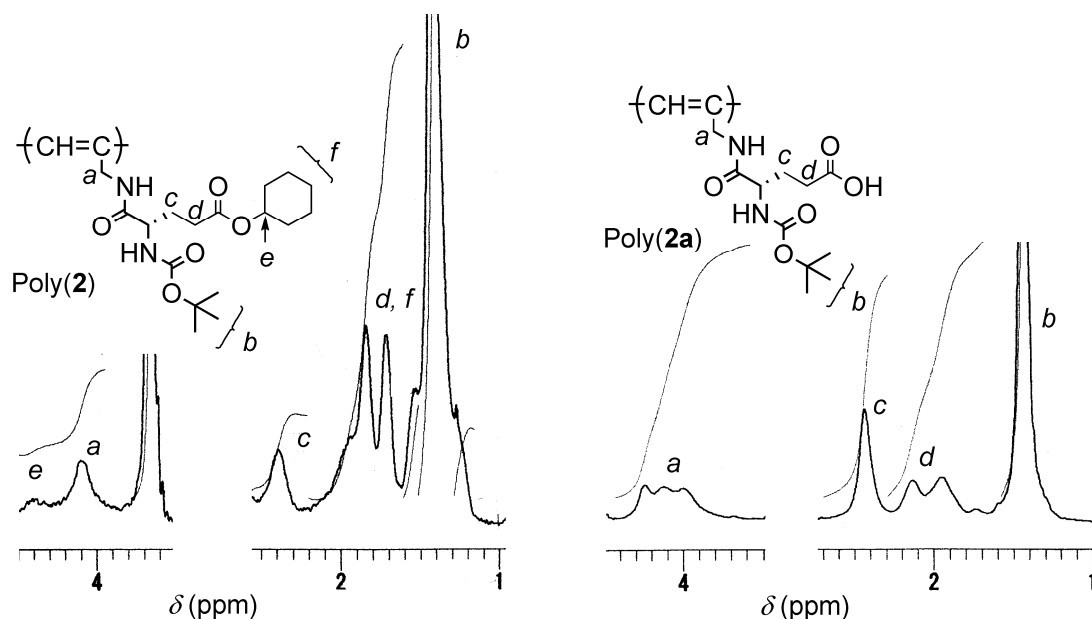


Figure 4. Partial ^1H NMR spectra of poly(**2**) measured in CDCl_3 and poly(**2a**) measured in CD_3OD .

As shown in Figure 1, poly(**1a**) obtained by hydrolysis of poly(**1**) exhibited no CD signal around 260 nm where poly(**1**) exhibited the Cotton effect. Meanwhile, poly(**1a**) exhibited a UV-vis absorption peak at 320 nm, which is assignable to randomly coiled polyacetylene backbone.¹⁴ This result indicates that the hydrolysis of the ester moiety of poly(**1**) resulted in transformation of helical structure into random coil. It is considered that electrostatic repulsion between the carboxyl groups is unfavorable to stabilize the helix. On the contrary, poly(**2a**) obtained by hydrolysis of poly(**2**) exhibited a CD signal and UV-vis absorption around 400 nm. Comparing the intensities of the CD and UV-vis peaks before and after hydrolysis (before: $-23\,683\text{ deg cm}^2\text{ dmol}^{-1}$ and $4\,378\text{ M}^{-1}\text{ cm}^{-1}$, after: $-5\,138\text{ deg cm}^2\text{ dmol}^{-1}$ and $3\,196\text{ M}^{-1}\text{ cm}^{-1}$; both decreased to 78% and 27% of the original ones by hydrolysis), it seems that the polymer still remained in a helical form after hydrolysis, but decreased the degree of predominance of one-handedness of screw sense. Random coiled structure should

be contaminated in poly(**2a**) to some extent, because a small absorption peak was present around 320 nm in the UV-vis spectrum.¹⁴

Figure 5 shows the CD and UV-vis spectra of poly(**2a**) measured in THF/MeOH with various compositions. The minus CD signal gradually turned into a plus one upon raising MeOH content. No CD spectroscopic change occurred after more than 20% MeOH was added. Thus we can say that poly(**2a**) inverted the helical sense by the addition of MeOH, because the CD signal is based on the conjugated polyacetylene backbone.¹⁵ Since the UV-vis absorption was observed around 400 nm in all cases,^{7,14} it is concluded that the helix inversion of poly(**2a**) did not take place *via* random coil but directly from helix to helix.

Figure 6 depicts the change of CD and UV-vis spectra upon addition of KOH to a solution of poly(**2a**) in THF/MeOH = 1/1 (v/v). The CD signal around 400 nm gradually decreased in conjunction with the UV-vis absorption by raising the amount of KOH. Further addition of KOH brought about the appearance of a new CD signal at 340 nm. These results suggest that poly(**2a**) transformed the conformation into another helix with different tightness and opposite sense to the initial one. This transformation seems to be caused by the difference of electrostatic repulsion between carboxyl and carboxylate anion groups. After the addition of 1.5 equivalent of KOH to the solution of poly(**2a**), HCl was added to the resulting solution. The CD spectroscopic pattern completely returned to the one before KOH addition. Thus, we could confirm the reversible conformational change of poly(**2a**) according to pH. The specific rotations of poly(**2a**) measured in THF, THF/MeOH = 1/1 (v/v), and THF/MeOH in the presence of 1.5 equiv of KOH were -369° , $+315^\circ$, and -158° , respectively. The much large values compared to **2a** (-3° , -6° , and -9° in these solvents), and the signs strongly support the assumption on the helical senses of poly(**2a**) in these solvents.

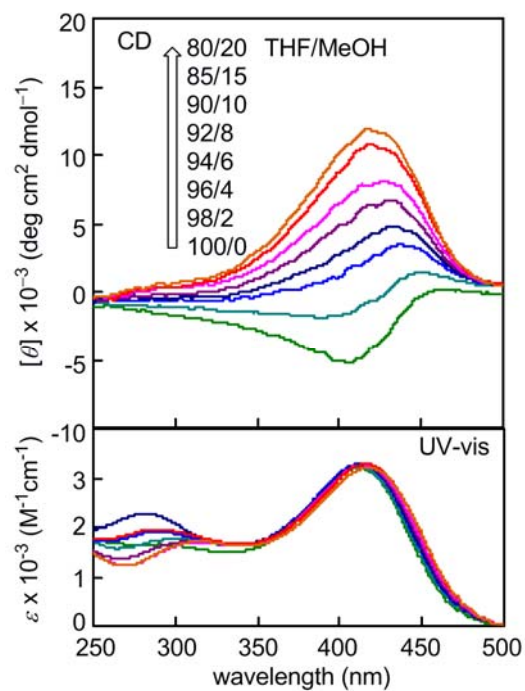


Figure 5. CD and UV-vis spectra of poly(**2a**) measured in THF/MeOH ($c = 0.5$ mM) with various compositions at 0 °C.

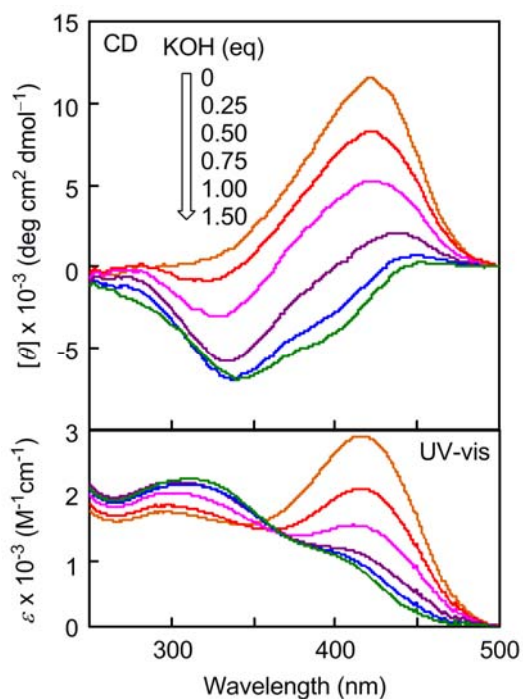


Figure 6. Change of CD and UV-vis spectra of poly(**2a**) upon addition of KOH measured in THF/MeOH = 1/1 (v/v, $c = 0.5$ mM) at 0 °C.

Table 2. IR Absorption (Amide I) of **1a, **2a**, Poly(**1a**), and Poly(**2a**)^a**

compound	wavenumber (cm ⁻¹)		
	in THF/MeOH		
	in THF	in THF/MeOH	with 1.5 equiv of
1a	1686	1665	— ^b
poly(1a)	1650	1655	— ^b
2a	1686	1672	— ^c
poly(2a)	1647	1653	1653

^a Reagent concentration 50 mM. ^b Not measured. ^c Could not be measured because the sample was insoluble.

Table 2 summarizes the liquid state IR spectroscopic data of C=O stretching of the amide groups of **1a**, **2a**, poly(**1a**), and poly(**2a**) measured in THF and THF/MeOH = 1/1 (v/v) in the absence and presence of 1.5 equiv of KOH. Poly(**2a**) exhibited the amide I absorption peak at 1647 cm⁻¹ in THF, which was 39 cm⁻¹ lower than that of **2a**. Judging from the low reagent concentration (50 mM), it is concluded that poly(**2a**) forms intramolecular hydrogen bonding between the amide groups. A similar result was observed in THF/MeOH. In this case, the efficiency of intramolecular hydrogen bonding should be lower than that in THF, because the difference between **2a** and poly(**2a**) was diminished to 19 cm⁻¹. This is likely to result from intermolecular hydrogen bonding between the amide groups and MeOH molecules. When 1.5 equiv of KOH was added to the solution of **2a** in THF/MeOH, the potassium salt of **2a** precipitated as white powder and the IR could not be measured. Meanwhile, no precipitate formed from the solution of poly(**2a**) by the addition of KOH. It seems

that the degree of neutralization of poly(**2a**) was lower than that of **2a**, which resulted in this difference. Since poly(**2a**) exhibited the amide I absorption peak at the same wavenumber in the absence and presence of KOH, it is considered that poly(**2a**) forms intramolecular hydrogen bonding similarly in both cases. Poly(**1a**) also exhibited the amide I absorption peaks at the lower wavenumber than those of **1a**. Intramolecular hydrogen bonding should exist, but it seems to be random one. In fact, the degrees of shift of wavenumber are smaller than those in **2a** and poly(**2a**).

Conclusion

In this chapter, the author has demonstrated the polymerization of L-aspartic and L-glutamic acid-based novel *N*-propargylamides **1** and **2** with a rhodium catalyst. The polymerization satisfactorily proceeded to give the corresponding polymers [poly(**1**) and poly(**2**)], which showed strong Cotton effects. Liquid state IR spectroscopic measurement revealed that they take helical conformations stabilized by intramolecular hydrogen bonding at the amide-amide and carbamate-carbamate moieties. They were satisfactorily converted into the corresponding polymers [poly(**1a**) and poly(**2a**)] with free carboxyl groups by alkaline hydrolysis. Poly(**1a**) did not form a helix, while poly(**2a**) took helical structure, which was responsive to the composition of THF and MeOH as a mixed solvent. Poly(**2a**) changed the helical sense and tightness in THF/MeOH = 1/1 (v/v) by the addition of KOH, presumably based on the difference of electronic repulsion between the carboxylate groups. By the addition of HCl, the polymer changed the helical sense and tightness again to recover the conformation before KOH addition. The author could thus successfully construct a pH-responsive system reversibly undergoing transformation of helical structure.

Experimental Section

Measurements. ^1H NMR spectra were recorded on a JEOL EX-400 spectrometer. IR spectra were measured using a Shimadzu FTIR-8100 spectrophotometer. Melting points (mp) were measured on a Yanaco micro melting point apparatus. Elemental analysis was done at the Kyoto University Elemental Analysis Center. Mass spectra were measured on a JEOL JMS-HX110A mass spectrometer. Specific rotations ($[\alpha]_{\text{D}}$) were measured on a JASCO DIP-100 digital polarimeter with a sodium lamp as a light source. The number- and weight-average molecular weights (M_n and M_w) of polymers were determined by gel permeation chromatography (GPC) on a JASCO Gulliver system (PU-980, CO-965, RI-930, and UV-1570) equipped with polystyrene gel columns (Shodex columns K804, K805, and K806), using THF as an eluent at a flow rate of 1.0 mL/min, calibrated by polystyrene standards at 40 °C. CD and UV-vis spectra were measured in a quartz cell (thickness: 1 cm) at room temperature using a JASCO J-820 spectropolarimeter.

Materials. All the reagents in monomer synthesis were used as purchased without purification. $(\text{nbd})\text{Rh}^+[\eta^6\text{-C}_6\text{H}_5\text{B}^-(\text{C}_6\text{H}_5)_3]$ (nbd = 2,5-norbornadiene) was prepared by the reaction of $[(\text{nbd})\text{RhCl}]_2$ with $\text{NaB}(\text{C}_6\text{H}_5)_4$ as described in the literature.¹⁶ THF used for polymerization was distilled by the standard procedure.

Monomer Synthesis. *N-tert-Butoxycarbonyl-O-cyclohexyl-L-aspartic acid N'-propargylamide (1)* *N*-Methylmorpholine (8.05 g, 79.3 mmol) and isobutyl chloroformate (10.8 g, 79.1 mmol) were added to a solution of *N-tert*-butoxycarbonyl-*O*-cyclohexyl-*L*-aspartic acid (25.0 g, 79.3 mmol) in THF (450 mL) at room temperature.¹⁷ Then, propargylamine (4.36 g, 79.3 mmol) was added to the mixture at 0 °C, and the resulting mixture was stirred at room temperature overnight. Precipitate formed was filtered off, and the filtrate was concentrated by rotary evaporation. The residual mass was dissolved in ethyl acetate (400 mL), and

the solution was washed with water (400 mL) three times. The organic layer was separated and dried over anhydrous MgSO_4 , and concentrated. The residue was purified by recrystallization with hexane/ethyl acetate = 2/1 (v/v) to obtain **1** as white powder. Yield 23.8 g (82%). Mp 104–105 °C, $[\alpha]_D -16.9^\circ$ ($c = 0.131$ g/dL in THF at room temperature). ^1H NMR (400 Hz, CDCl_3): δ 1.44 [s, 15H, $(\text{CH}_3)_3$, $(\text{CH}_2)_3$], 1.70 [m, 2H, $\text{OCH}(\text{CH}_2)$], 1.83 [m, 2H, $\text{OCH}(\text{CH}_2)$], 2.22 [s, 1H, $\text{HC}\equiv$], 2.66 [m, 1H, CHCH_2], 2.96 [m, 1H, CHCH_2], 4.04 [s, 2H, CH_2], 4.49 [s, 1H, CHNH], 4.77 [m, 1H, OCH_2], 5.66 [s, 1H, NHCOO], 6.74 [s, 1H, NHCO]. ^{13}C NMR (100 MHz, CDCl_3): δ 24.35 [$\text{OCHCH}_2\text{CH}_2$], 25.95 [$\text{OCHCH}_2\text{CH}_2\text{CH}_2$], 28.97 [$(\text{CH}_3)_3$], 29.97 [OCHCH_2], 32.15 [CH_2], 37.01 [CHCH_2], 51.27 [NHCH], 72.32 [$\text{HC}\equiv$], 74.37 [$\text{C}(\text{CH}_3)_3$], 79.80 [OCH], 81.23 [$\text{CH}_2\text{C}\equiv$], 156.20 [$\text{C}(\text{CH}_3)_3\text{OCO}$], 171.13 [COO], 171.83 [NHCO]. IR (cm^{-1} , KBr): 3248 ($\text{H}-\text{C}\equiv$), 2126 ($\text{H}-\text{C}\equiv$), 1734 ($\text{C}=\text{O}$), 1687 (NHCOO), 1664 (NHCO), 1538, 1509, 1252, 1184, 1055, 1011, 710, 660. HRMS Calcd for $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_5$ (m/z) 353.2076. Found: 353.2082.

N-tert-Butoxycarbonyl-O-cyclohexyl-L-glutamic acid N'-propargylamide

(2) The title compound was synthesized from *N-tert-butoxycarbonyl-O-cyclohexyl-L-glutamic acid* and propargylamine in a manner similar to **1**. Yield 19%. Mp 107–108 °C, $[\alpha]_D -14.6^\circ$ ($c = 0.098$ g/dL in THF at room temperature). ^1H NMR (400 Hz, CDCl_3): δ 1.44 [s, 9H, $(\text{CH}_3)_3$], 1.61 [m, 6H, $(\text{CH}_2)_3$], 1.73 [m, 2H, $\text{OCH}(\text{CH}_2)$], 1.84 [m, 2H, $\text{OCH}(\text{CH}_2)$], 1.94 [t, $J = 8.00$ Hz, 1H, CH_2CO], 2.11 [t, $J = 8.00$ Hz, 1H, CH_2CO], 2.23 [s, 1H, $\text{HC}\equiv$], 2.35 [m, 1H, CHCH_2CH_2], 2.48 [m, 1H, CHCH_2CH_2], 4.04 [s, 2H, CH_2], 4.14 [s, 1H, CHNH], 4.77 [s, 1H, OCH_2], 5.25 [s, 1H, NHCOO], 6.57 [s, 1H, NHCO]. ^{13}C NMR (100 MHz, CDCl_3): δ 24.04 [$\text{OCHCH}_2\text{CH}_2$], 25.62 [$\text{OCH}_2\text{CH}_2\text{CH}_2$], 27.97 [CHCH_2CH_2], 28.58 [CHCH_2CH_2], 29.47 [$(\text{CH}_3)_3$], 31.23 [$\text{OCH}(\text{CH}_2)$], 31.90 [CH_2], 71.98 [$\text{HC}\equiv$], 73.52 [OCH], 79.43 [$\text{CH}_2\text{C}\equiv$], 173.09 [$\text{C}(\text{CH}_3)_3\text{OCO}$], 183.53 [COO], 186.55 [NHCO]. IR

(cm⁻¹, KBr): 3262 (H-C≡), 1728 (C=O), 1694 (NHCOO), 1659 (NHCO), 1454, 1308, 1198, 1102, 1009, 722, 685. Anal. Calcd for C₁₉H₃₀N₂O₅: C, 62.27; H, 8.25; N, 7.64. Found: C, 62.16; H, 8.26; N, 7.53.

Polymerization. The polymerization was carried out in a glass tube equipped with a three-way stopcock under nitrogen. (nbd)Rh⁺[η^6 -C₆H₅B⁻(C₆H₅)₃] (10.3 mg, 0.02 mmol) was added to a solution of a monomer (1.0 mmol) in THF (5.0 mL), and the resulting mixture was vigorously stirred. It was kept in a water bath at 30 °C for 1 h. The resulting mixture was poured into *n*-hexane (250 mL) to precipitate a polymer. It was separated by filtration using a membrane filter (ADVANTEC H100A047A), and dried under reduced pressure.

Alkaline Hydrolysis of the Polymers. To a solution of poly(**1**) (619 mg, 1.76 mmol) in THF (10 mL), 1 M NaOH aqueous solution (2.3 mL, 2.3 mmol) was added at 0 °C, and the resulting mixture was stirred at 50 °C for 2.5 h. The reaction mixture was acidified with 0.5 M solution of citric acid in methanol (45 mL), and concentrated by rotary evaporation. The resulting mixture was poured into water (300 mL) to precipitate poly(**1a**). It was separated by filtration using a membrane filter (ADVANTEC H100A047A), and dried under reduced pressure.

Spectroscopic Data of the Polymers. **Poly(1)**; ¹H NMR (400 Hz, CDCl₃): δ 1.41 [br, 15H, (CH₃)₃, (CH₂)₃], 1.75 [br, 4H, OCH(CH₂)₂], 2.83 [br, 2H, CH₂CO], 4.11 [s, 1H, HC=], 4.73 [br, 3H, CH, CH₂], 6.10 [br, 1H, NHCOO], 7.94 [br, 1H, NHCO]. IR (cm⁻¹, KBr): 3351 (NHCO), 2940 (CH), 1728 (C=O), 1655 (NHCO), 1173, 1049, 1017. **Poly(2)**; ¹H NMR (400 Hz, CDCl₃): δ 1.42 [br, 15H, (CH₃)₃, (CH₂)₃], 1.72 [br, 2H, OCH(CH₂)], 1.83 [br, 2H, OCH(CH₂)], 2.36 [br, 2H, CH₂CO], 3.49 [s, 1H, HC=], 4.05 [br, 1H, CH], 4.73 [br, 2H, CH₂]. IR (cm⁻¹, KBr): 3292 (NHCO), 2940 (CH), 1717 (C=O), 1647 (NHCO), 1173, 1046, 1019. **Poly(1a)**; ¹H NMR (400 Hz, CD₃OD): δ 1.44 [br, 9H, (CH₃)₃], 2.86 [br, 2H, CH₂CO], 3.96 [br, 2H, CH₂C≡C], 4.55

[br, 1H, CHNH], 6.16 [br, 1H, NH]. IR (cm⁻¹, KBr): 3336 (NHCO), 2980 (CH), 1717 (C=O), 1655 (NHCO). **Poly(2a)**; ¹H NMR (400 Hz, CD₃OD): δ 1.44 [br, 9H, (CH₃)₃], 4.12 [br, 2H, CH₂C≡C], 4.23 [br, 1H, CHNH], 6.18 [br, 1H, NH].

References and Notes

- (1) Gil, E. S.; Hudson, S. M. *Prog. Polym. Sci.* **2004**, 29, 1173.
- (2) Merutka, G.; Stellwagen, E. *Biochemistry* **1991**, 30, 1591.
- (3) (a) Gao, G.; Sanda, F.; Masuda, T. *Macromolecules* **2003**, 36, 3932. (b) Gao, G.; Sanda, F.; Masuda, T. *Macromolecules* **2003**, 36, 3938.
- (4) Sanda, F.; Araki, H.; Masuda, T. *Macromolecules* **2004**, 37, 8510.
- (5) Tabata, M.; Sone, T.; Sadahiro, Y. *Macromol. Chem. Phys.* **1999**, 200, 265.
- (6) Deng, J.; Tabei, J.; Shiotsuki, M.; Sanda, F.; Masuda, T. *Macromolecules* **2004**, 37, 1891.
- (7) Nomura, R.; Tabei, J.; Masuda, T. *J. Am. Chem. Soc.* **2001**, 123, 8430.
- (8) Percec, V.; Obata, M.; Rudick, J. G.; De, B. B.; Glodde, M.; Bera, T. K.; Magonov, S. N.; Balagurusamy, V. S. K.; Heiney, P. A. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, 40, 3509.
- (9) (a) Akieda, T.; Mimura, H.; Kuroki, S.; Kurosu, H.; Ando, I. *Macromolecules* **1992**, 25, 5794. (b) Saito, H.; Tabeta, R.; Ando, I.; Ozaki, T.; Shoji, A. *Chem. Lett.* **1983** 1437.
- (10) Shoji, A.; Ozaki, T.; Saito, H.; Tabeta, R.; Ando, I. *Macromolecules* **1984**, 17, 1472.
- (11) Halgren, T. A. *J. Comput. Chem.* **1996**, 17, 490. All the calculations were carried out with MMFF94 force field, using Wavefunction, Inc. Spartan '04 Windows version 1.01.
- (12) Saito, M. A.; Maeda, K.; Onouchi, H.; Yashima, E. *Macromolecules* **2000**, 33, 4616.
- (13) Poly(**2**) was soluble in CDCl₃ and insoluble in CD₃OD, while poly(**2a**) was soluble in CD₃OD and insoluble in CDCl₃. We also tried DMSO-*d*₆ but neither of the polymers was soluble in the solvent.
- (14) Nomura, R.; Tabei, J.; Masuda, T. *Macromolecules* **2002**, 35, 2955.
- (15) It has recently been reported that side chain reorientations of helical polyguanidines can be driven by temperature, solvent polarity or preferential solvation. They show a change in sign of the Cotton effect by just a reorientation of the anthracene side chains with no change in helical sense (Tang, H.-Z.; Boyle, P. D.; Novak, B. M. *J. Am. Chem. Soc.* **2005**, 127, 2136),

wherein the CD signal does not come from the main chain but does from the side chain, different from the present study.

- (16) Schrock, R. R.; Osborn, J. A. *Inorganic Chem.* **1970**, 9, 2339.
- (17) Brosch, O.; Weyhermüller, T.; Metzler-Nolte, N. *Inorg. Chem.* **1999**, 38, 5308.

Chapter 2

Synthesis and Secondary Structure of Polyacetylenes Carrying Diketopiperazine Moieties. The First Example of Helical Polymers Stabilized by *s-cis* Amide-based Hydrogen Bonding

Abstract

Novel optically active phenylacetylenes having diketopiperazine were synthesized from L-phenylalanine and polymerized with a rhodium catalyst to obtain the polymers with number-average molecular weights over 10 000 in good yields. The CD and UV-vis spectra of the polymers indicated that they took helical structures with predominantly one-handed screw sense in DMF, while random coil structures in CHCl_3 . Addition of various carboxylic acids such as trifluoroacetic acid to the polymer solution in CHCl_3 promoted the helical formation. Molecular mechanics calculation suggested that the most stable conformer was a right-handed helix accompanying tandem hydrogen-bonding strands between the amide groups.

Introduction

Diketopiperazine (DKP), a cyclic dimer of amino acids, is a typical by-product in peptide synthesis. DKPs are studied as bioactive and enzyme-inhibitory compounds in a manner similar to linear peptides.¹ DKP has two *s-cis* secondary amide groups, which can hydrogen bond horizontally along the ring plane. Some DKPs form aggregates based on tandem hydrogen bonding between the amide groups in the solid state. The way of aggregation depends on the amino acid components of DKPs. For example, a glycine-based DKP adopts a linear tape orientation, while an alanine-based one forms a layer-type structure.² DKP is poorly soluble in organic solvents due to the rigid cyclic structure bearing amide groups. *N*-Alkylation of one amide group effectively enhances the solubility, leading to a change of association state.³ This type of DKP constructs supramolecular architectures including liquid crystals⁴ and microcapsules⁵ utilizing noncovalent bonding such as hydrophobic and electrostatic interactions in addition to hydrogen bonding between the amide groups. Phenylalanine-, aspartic and glutamic acid-based DKPs serve as oil gelators,⁶ wherein intermolecular hydrogen bonding plays a key role to form molecular networks. Unsymmetrical DKPs consisting of phenylalanine together with histidine or arginine are used as an organocatalyst for asymmetric hydrocyanation.⁷

Although DKP derivatives have several interesting features as described above, polymers carrying DKPs have been scarcely synthesized, and the molecular weights and the detail of the properties have not been well determined.⁸ The author has recently reported the polycondensation of aspartic and glutamic acid DKPs with diamines and dibromoxylenes to give polymers with moderate molecular weights.⁹ The author has also reported the acyclic diene metathesis polycondensation of glutamic acid DKP ω -alkenyl esters with ruthenium catalysts. The formed polymers are associated in the solid and solution states based on hydrogen bonding between the

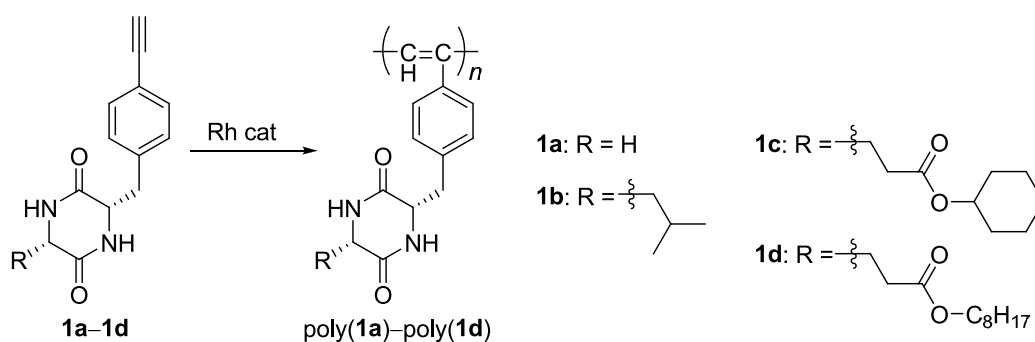
DKP moieties.¹⁰ However, the polymers do not show the evidence of formation of a chiral secondary structure, presumably due to the insufficient control over the stereoregularity (*cis* and *trans*) as well as the presence of non-rigid alkylene spacers in the main chain.

Among various polymers having double bonds in the main chain, substituted polyacetylenes synthesized by the polymerization with iron-aluminum and rhodium catalysts feature a highly *cis*-stereoregular structure.¹¹ Introduction of appropriate chiral substituents to *cis*-polyacetylenes leads to the formation of a helical structure with predominantly one-handed screw sense. A pioneering work on substituted helical polyacetylenes has been done by Ciardelli et al. in the 1970s. They have reported that polyacetylenes having chiral aliphatic side chains synthesized by iron tris(acetylacetonate)-aluminum triisobutyl catalyst take a helical conformation in solution.^{11a} Since [Rh(norbornadiene)Cl]₂–triethylamine catalyst was found to polymerize monosubstituted acetylenes to give *cis*-stereoregular polymers satisfactorily,¹² many studies regarding substituted helical polyacetylenes synthesized by rhodium catalysts have been reported so far.¹³

Masuda and coworkers have reported that *cis*-stereoregular polyacetylene derivatives carrying amide groups such as poly(*N*-propargylamide)s,¹⁴ poly(*N*-propargylsulfamide)s, poly(*N*-propargylphosphonamidate)s,¹⁵ and poly(*N*-butynylamide)s¹⁶ form helical structures with predominantly one-handed screw sense, which are stabilized by regulated intramolecular hydrogen bonding between the amide groups as well as steric repulsion in the biomimetically same way as peptides and proteins. They change the conformation by external stimuli such as heat and the addition of polar solvents, which disturb the formation of intramolecular hydrogen bonding stabilizing the helical structure. It is likely that all the amide moieties take an *s-trans* structure in the aforementioned helical polymers. On the other hand, no

example has been reported regarding polyacetylenes carrying quantitatively *s-cis* amide moieties in the side chains as far as we know. It is expected that such *s-cis* amide-based polymers exhibit behavior different from that of *s-trans* amide-based ones. The present chapter deals with the synthesis and polymerization of novel phenylacetylenes **1a–1d** having DKP moieties consisting of *s-cis* amide (Scheme 1), and examination of the secondary structure of the resultant polymers that possibly form regulated intramolecular hydrogen bonding between the amide groups.

Scheme 1

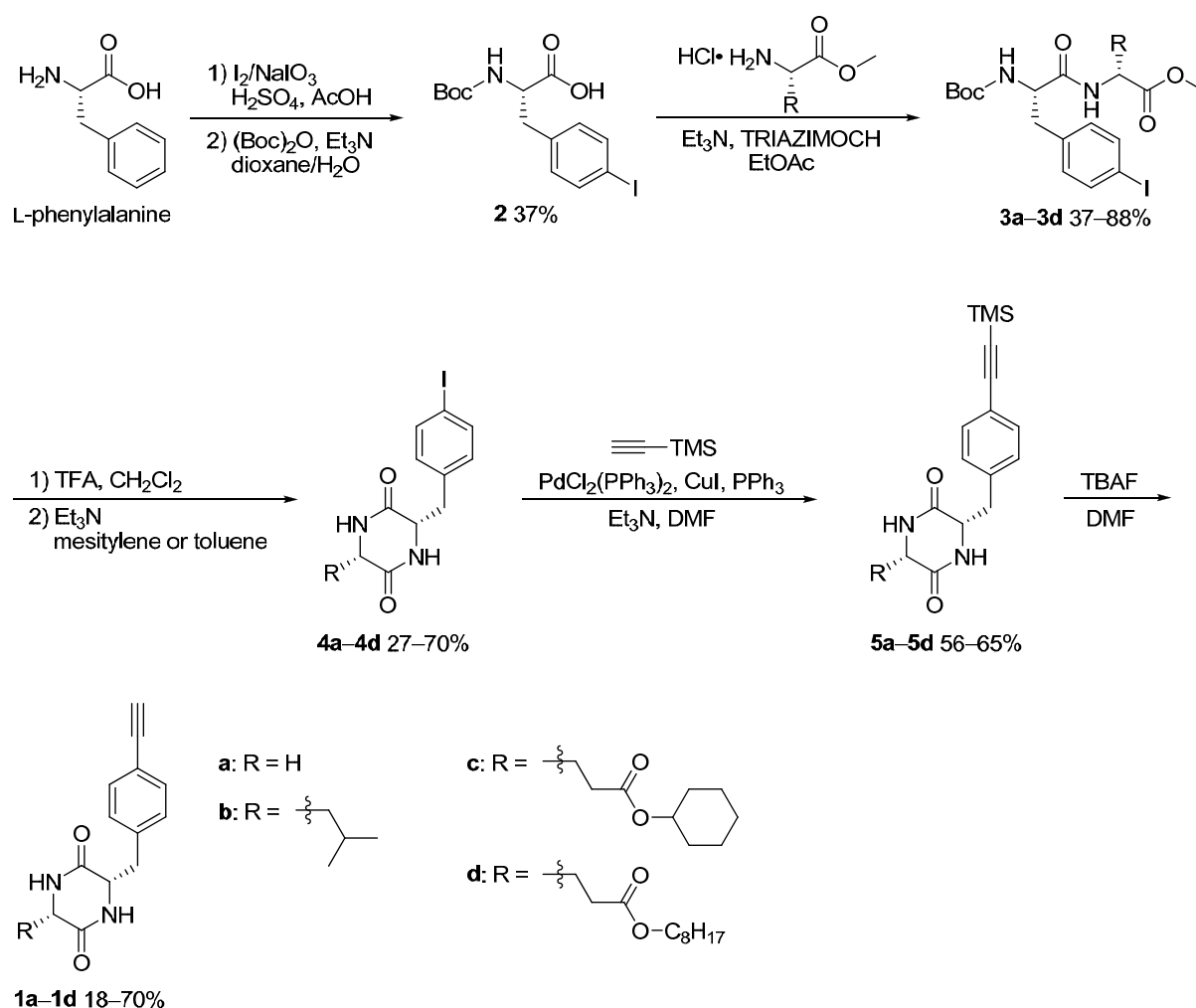


Results and Discussion

Monomer Synthesis. Monomers **1a–1d** were synthesized via the corresponding linear dipeptides according to the route illustrated in Scheme 2. Namely, the amino group of 4-iodinated-L-phenylalanine was protected with Boc group, followed by condensation with the corresponding amino acid methyl ester hydrochlorides to obtain dipeptides **3a–3d**. After the deprotection of *N*-terminal site with TFA, the residue was dissolved in a hydrocarbon solvent (mesitylene or toluene) at a low reagent concentration (ca. 40 mM), followed by heating for 6 h to promote the cyclization through intramolecular ester-amide exchange reaction of the liner dipeptides to obtain DKPs **4a–4d**. Gelation occurred in toluene in the case of **4d**, which was presumably due to the aggregation through hydrogen bonding between the

amide groups and van der Waals interaction between the long alkyl chains as reported by Hanabusa et al.⁶ It is expected that a similar interaction might be observed between the side chains of the polymers. Subsequently, the Sonogashira coupling reaction of the 4-iodinated-L-phenylalanine-derived DKPs with TMS acetylene, and desilylation of the protected ethynyl group were carried out to obtain monomers **1a–1d**. Monomers **1a** and **1b** were soluble in MeOH, DMF, and DMSO, while insoluble in CHCl₃. Monomers **1c** and **1d** were soluble in all these solvents.

Scheme 2



Synthesis and Secondary Structures of the Polymers. Table 1 summarizes

the conditions and results of the polymerization of DKP-containing phenylacetylenes **1a–1d** catalyzed with (nbd)Rh⁺[η^6 -C₆H₅B[−](C₆H₅)₃] in DMF (Scheme 1). The corresponding polymers were isolated as methanol-insoluble parts in good yields. In the polymerization of **1a** and **1b**, the polymers began precipitating in a little while after initiating the polymerization. Poly(**1a**) and poly(**1b**) isolated were insoluble in common organic solvents such as DMF. Meanwhile, poly(**1c**) and poly(**1d**) with M_n 's of 15500 and 54600 were soluble in DMF and CHCl₃. The specific rotations were −119° and −190°, respectively, both of which were much larger than those of the monomers (−34° and −3°).

Table 1. Polymerization of 1a–1d ^a

monomer	polymer				
	$[\alpha]_D^b$ (deg)	yield ^c (%)	M_n^d	M_w/M_n^d	$[\alpha]_D^b$ (deg)
1a	−2	100	— ^e	— ^e	— ^e
1b	−34	79	— ^e	— ^e	— ^e
1c	−34	100	15500	3.38	−119
1d	−3	96	54600	3.07	−190

^a Catalyst: (nbd)Rh⁺[η^6 -C₆H₅B[−](C₆H₅)₃]; Conditions: [M]₀ = 0.20 M, [M]₀/[Cat] = 50 in DMF at 30 °C for 24 h. ^b Measured by polarimetry at room temperature, *c* = 0.10 g/dL in DMF. ^c MeOH-insoluble part. ^d Estimated by GPC based on polystyrene standards, eluent; LiBr solution in DMF (10 mM). ^e Could not be determined due to the insolubility in solvents.

Figure 1 depicts the CD and UV-vis spectra of poly(**1c**) and poly(**1d**) measured in DMF at 0–90 °C. At 0 °C, both polymers exhibited intense Cotton

effects at a UV-absorption area based on the conjugated main chain, suggesting that the polymers took helical structures with predominantly one-handed screw sense in the solvent. By raising the temperature, the intensity of the Cotton effects gradually decreased, while the UV-vis absorption peak slightly changed, indicating that the bias of the helical sense was reduced at higher temperature.

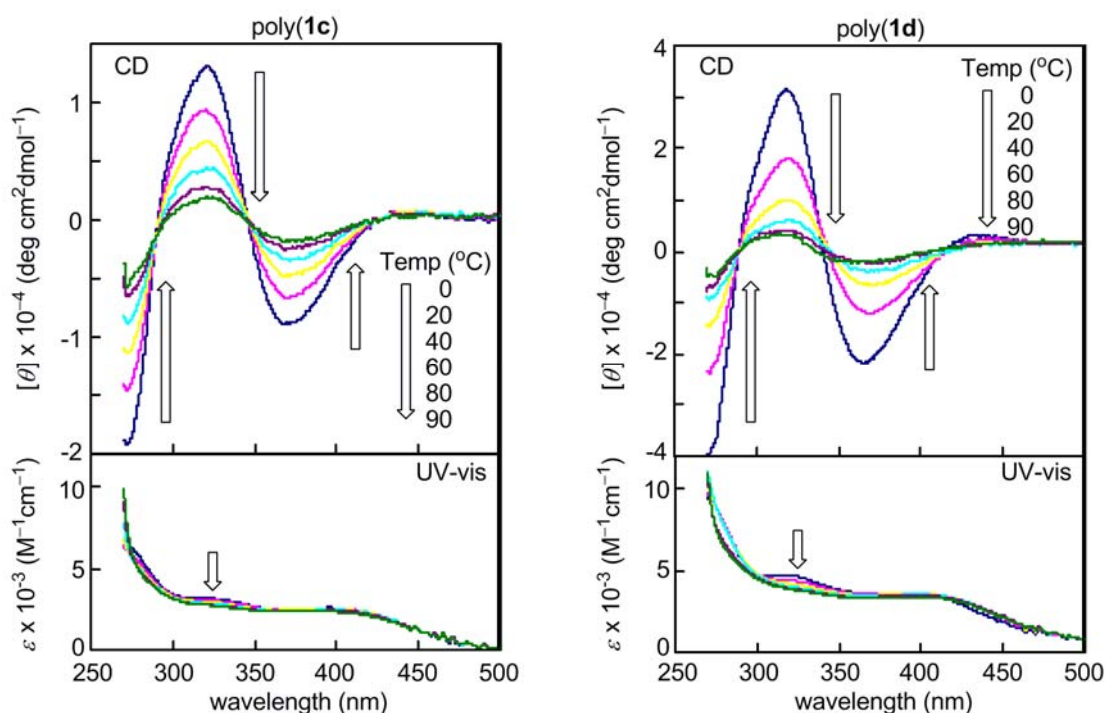


Figure 1. CD and UV-vis spectra of poly(**1c**) and poly(**1d**) measured in DMF ($c = 0.20$ mM) at 0 °C.

Figure 2 shows the CD and UV-vis spectra of poly(**1d**) measured in DMF/ CHCl_3 with various compositions. The CD signal gradually decreased in conjunction with the UV-vis absorption upon raising CHCl_3 content. The Cotton effects almost disappeared in CHCl_3 only. These spectral changes could also be monitored by color change of the solution from yellow to nearly no color. These results suggest that poly(**1d**) does not take a helical structure but a random coil structure in CHCl_3 . In a similar manner, it was confirmed that poly(**1c**) also took a random structure in CHCl_3 .

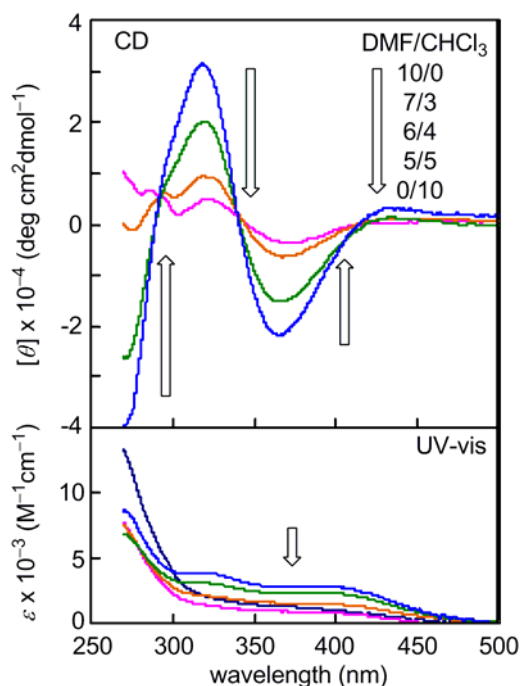


Figure 2. CD and UV-vis spectra of poly(**1d**) measured in DMF/CHCl₃ at 0 °C.

Effect of Additives. It has been reported that TFA interrupts hydrogen bonding between DKPs to disrupt the association.³ In the present chapter, hydrogen bonding also seems to play an important role in forming the secondary structure of the polymers. Thus, the author measured the CD and UV-vis spectra of poly(**1d**) in CHCl₃ upon addition of TFA (Figure 3) to check the effect on the secondary structure. As described above, the polymer showed no intense CD signal in CHCl₃. The addition of 300 equiv of TFA to the monomer unit brought about the appearance of CD signals and UV-vis absorption based on the polyacetylene main chain. A further increase in TFA amount (600 equiv) raised the intensities of the Cotton effect and UV-vis absorption. These results indicate that the addition of TFA promoted the helix formation of the polymer in CHCl₃, in which the polymer did not take a helical structure in the absence of TFA. Interestingly, the Cotton effect disappeared when 1200 equiv of TFA was added. The possibility of main chain fission of the polymer is negligible, which was confirmed by GPC measurement after TFA addition. In

contrast, TFA addition to a polymer solution in DMF did not affect the spectra.

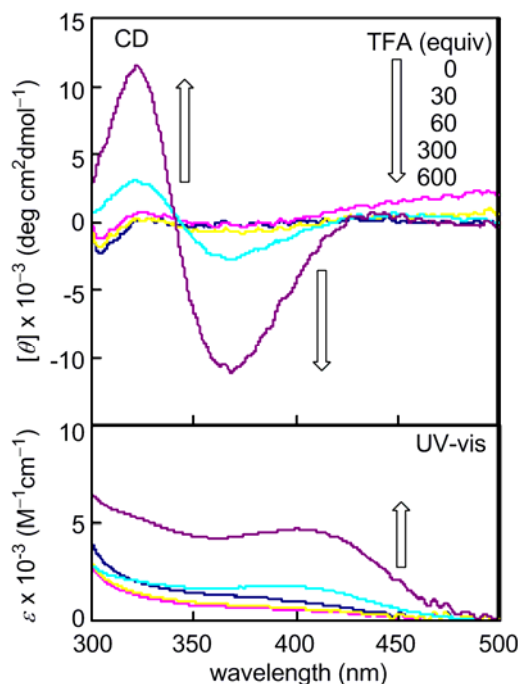


Figure 3. CD and UV-vis spectra of poly(**1d**) upon addition of TFA measured in CHCl_3 ($c = 0.20 \text{ mM}$) at 0°C .

Figure 4 depicts the CD and UV-vis spectra of poly(**1d**) measured in CHCl_3 upon addition of carboxylic acids with various pK_a values, acetic acid (AcOH , $\text{pK}_a = 4.76$), chloroacetic acid (CH_2ClCOOH , $\text{pK}_a = 2.87$), dichloroacetic acid (CHCl_2COOH , $\text{pK}_a = 1.48$), and trichloroacetic acid (CCl_3COOH , $\text{pK}_a = 0.70$). The intensity of the CD signals increased together with that of UV-absorption based on the conjugated main chain with addition of the carboxylic acids in all cases. It was suggested that these carboxylic acids induced the helical structure of the polymers in CHCl_3 in a manner similar to TFA ($\text{pK}_a = 0.30$). The additive amount, which induced the maximum intensity of the Cotton effects, depended on the acidity of the carboxylic acids ($\text{AcOH} > \text{CH}_2\text{ClCOOH}$, $\text{CHCl}_2\text{COOH} > \text{CCl}_3\text{COOH} > \text{TFA}$).

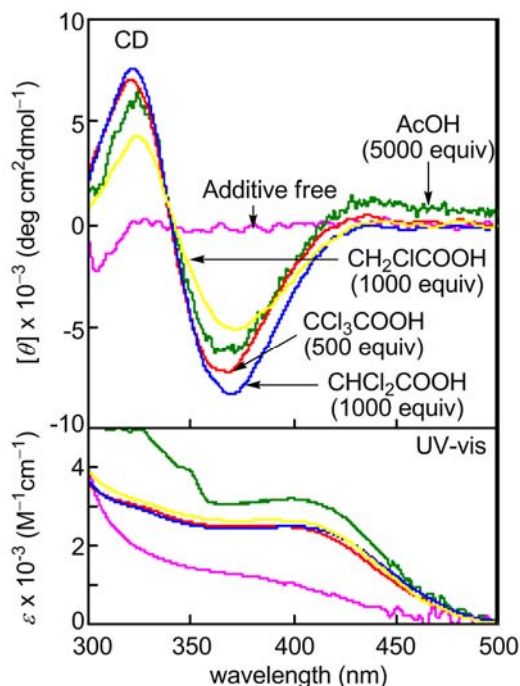


Figure 4. CD and UV-vis spectra of poly(**1d**) upon addition of various carboxylic acids measured in CHCl_3 ($c = 0.20 \text{ mM}$) at 0°C .

The addition of other carboxylic acids such as propionic and *tert*-butyric acid showed the same tendency. In contrast, the addition of tetra-*n*-butylammonium fluoride and δ -valerolactam to a solution of poly(**1d**) in CHCl_3 did not induce CD signals and change the UV-vis spectra at all. As noted above, addition of TFA to a polymer solution in DMF did not promote the helix formation of the polymers. These results brought the author the idea that the side chain took a conformation inducing a helix efficiently by some interaction such as hydrogen bonding between the side chain and either DMF or carboxylic acids such as TFA. The helical structures induced by addition of carboxylic acids are regarded as the same in form judging from the shapes of the CD signals. It seems that the addition of more than a certain amount of CCl_3COOH and CHCl_2COOH destroys the helical structures (Figure 5). It is assumed that the carboxylic acids below a certain amount form hydrogen bonding with the ester moieties of the DKP side chains to suppress the formation of random

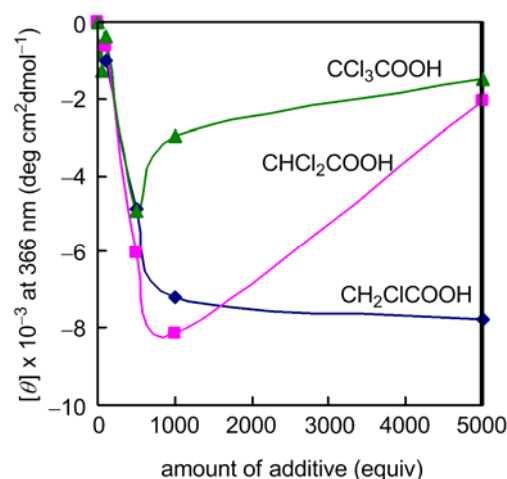


Figure 5. Plots of amount of additive vs. $[\theta]$ at 366 nm in the CD spectra of poly(**1d**) measured in CHCl_3 ($c = 0.20 \text{ mM}$) at 0°C .

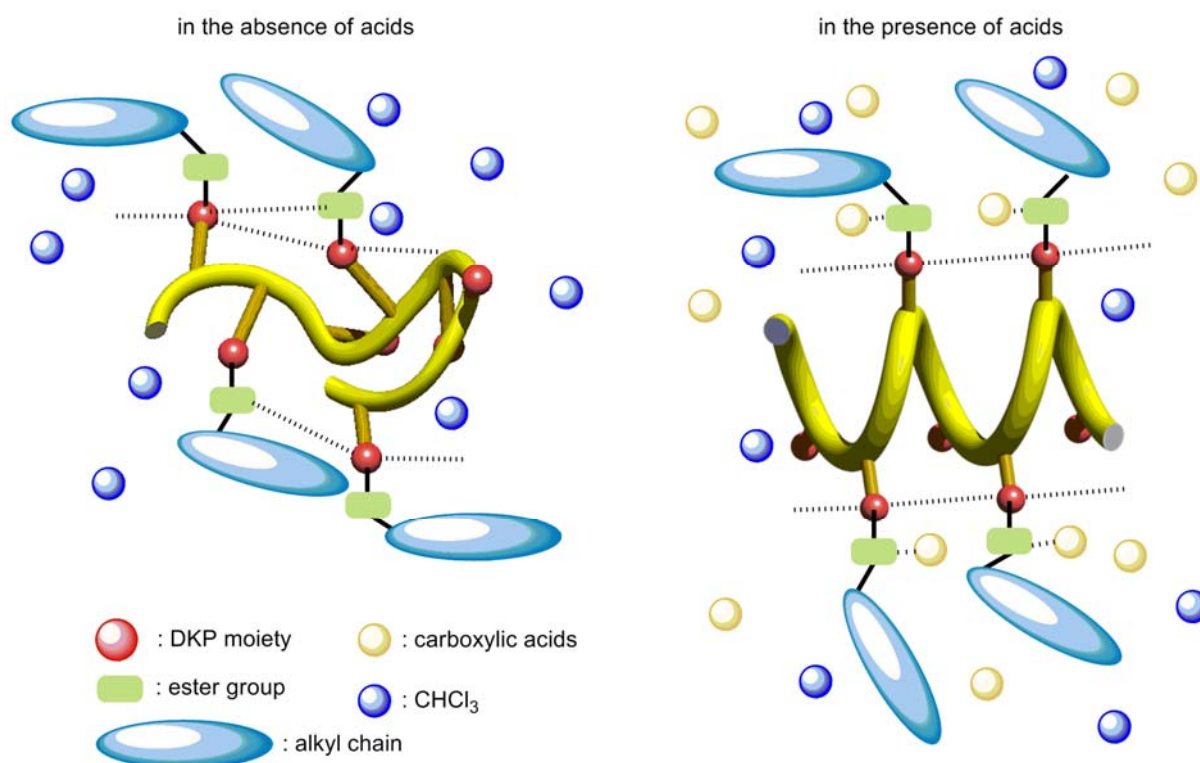


Figure 6. Proposed models of the manner of hydrogen bonding between the DKP moieties, ester groups, and carboxylic acids in CHCl_3 .

hydrogen bonding between the ester and amide groups of DKPs, leading to the formation of helical structure efficiently as illustrated in Figure 6. This assumption

agrees with the fact that the CD and UV-vis spectra were inactive for addition of δ -valerolactam, which has an *s-cis* amide group. However, too much carboxylic acid causes the collapse of the helical structure, presumably due to the formation of hydrogen bonding between the acids and amide groups of the DKP moieties, which disturbs the formation of regulated intramolecular hydrogen bonding between the DKP moieties. Meanwhile it is considered that, in DMF, the ester moieties mainly form intermolecular hydrogen bonding with DMF, and the DKP moieties form intramolecular hydrogen bonding between the side chains.

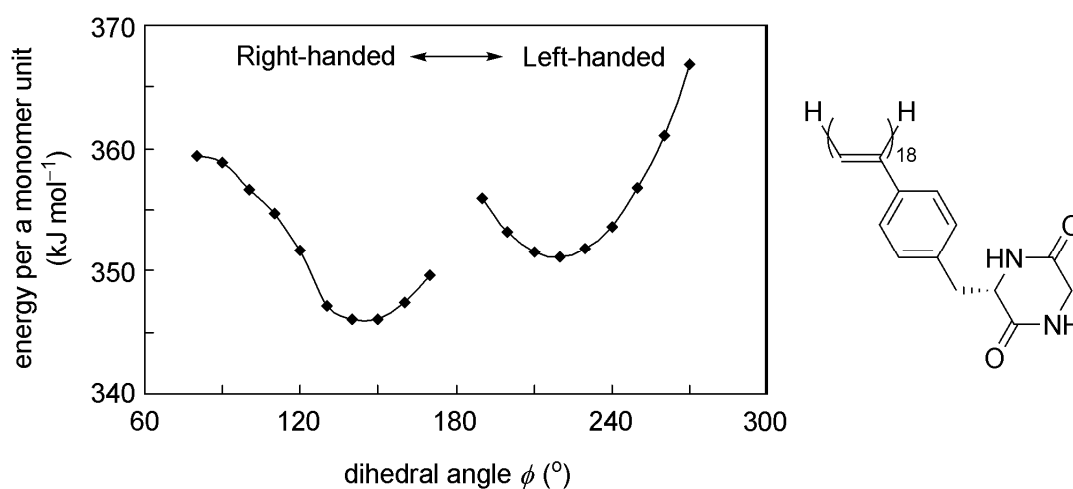


Figure 7. Relationship between the dihedral angle ϕ at the single bond of the main chain of poly(**1a**) (18-mer) and the energy calculated by MMFF94.

The author constructed molecular models of a helical 18-mer of **1a** based on the assumption that hydrogen bonding exists between the amide groups of DKPs. The dihedral angle at the double bond in the main chain was fixed at 0° (*cis*-polyacetylene), and the dihedral angle ϕ at the single bond was varied from 80° to 170° (right-handed helix) and 190° to 260° (left-handed helix) at every 10° increment. The geometries were optimized by the molecular mechanics calculation using the

MMFF94 force field¹⁷ to estimate the energy. As illustrated in Figure 7, the right-handed conformer at the energy minimum was 5.11 kJ/mol more stable per monomer unit than the left-handed one. As shown in Figure 8, the right-handed conformer with $\phi = 140$ was the most stable when hydrogen bonding was doubly formed between n th and $(n+2)$ th units. The main chain takes a helical conformation and the side chains are aligned helically. It should be noted that the helical polyacetylene main chain is right-handed, while the two helical arrays of the DKPs connected with hydrogen bonding strands are left-handed in a manner similar to helical poly(*N*-propargylamide)s.¹⁸

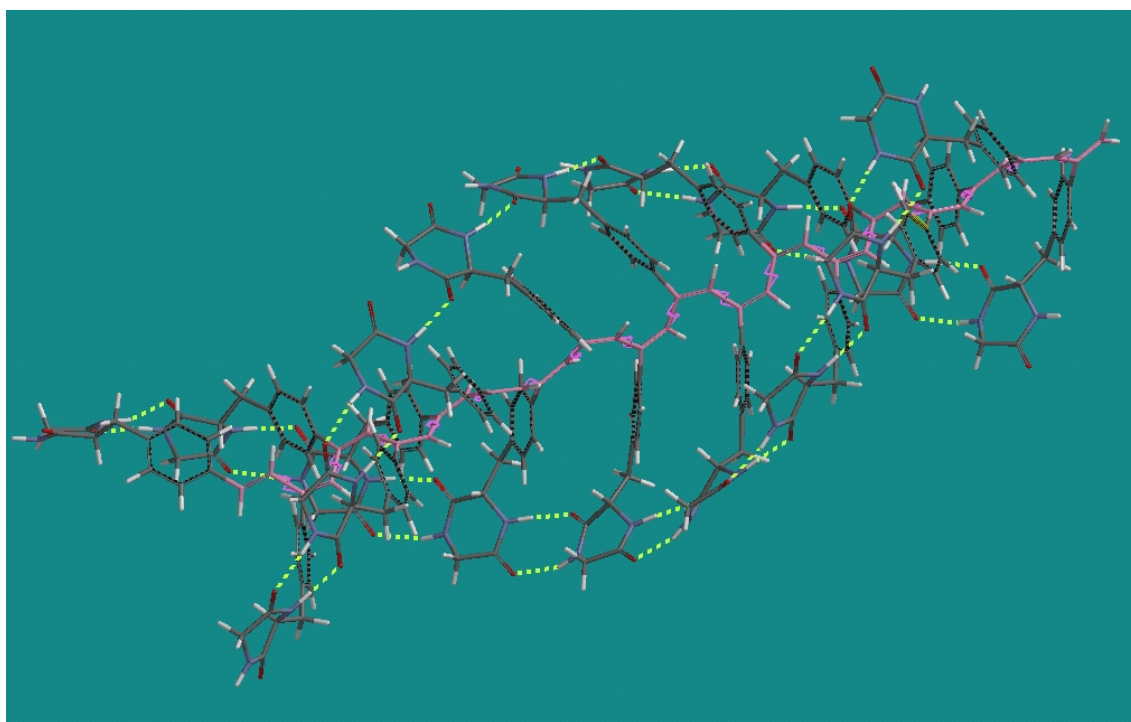


Figure 8. The most stable conformer of poly(**1a**) (18-mer) optimized by MMFF94.

Yashima and coworkers have determined the helix sense of cis-stereoregular poly(phenylacetylene)s from the atomic force microscopy images of the polymers deposited on highly oriented pyrolytic graphite from a dilute solution.¹⁹ They confirmed that the poly(phenylacetylene)s exhibiting a minus Cotton effect around 370

nm show a left-handed helical structure with respect to the pendant arrangements. The main chain of the poly(phenylacetylene)s takes a right-handed helical structure, since the screw sense of helically aligned side chains is opposite to that of the main chain.¹⁸ In the present study, poly(**1c**) and poly(**1d**) showed a minus Cotton effect around 370 nm as depicted in Figures 1–4. The screw sense of the main chain of the present polymers is right-handed according to the molecular mechanics calculation, which agrees with Yashima's report.¹⁹

Conclusion

In the present chapter, the author has demonstrated the synthesis and polymerization of novel optically active phenylacetylenes having DKP moieties using a rhodium catalyst to obtain the polymers with moderate molecular weights in good yields. They took helical structures with predominantly one-handed screw sense in DMF, while random one in CHCl₃. Addition of various carboxylic acids promoted the formation of helical structures in CHCl₃. As far as the author knows, this phenomenon is the first observation in synthetic helical polymers including polyacetylenes and polyisocyanides. This feature seems to be unique to substituted polyacetylenes whose helical structure is stabilized by the hydrogen bonding strands doubly formed between the *s-cis* amide-moieties of DKP side chains. The molecular mechanics calculation suggested that the most stable conformer is the right-handed one with $\phi = 140$ accompanying hydrogen bonding strands formed between *n*th and (*n*+2)th units.

Experimental Section

Measurements. ¹H and ¹³C NMR spectra were recorded on a JEOL EX-400 spectrometer. IR spectra were measured on a JASCO FT/IR-4100 spectrophotometer.

Melting points (mp) were measured on a Yanaco micro melting point apparatus. Mass spectra were measured on a JEOL JMS-HX110A mass spectrometer. Specific rotations ($[\alpha]_D$) were measured on a JASCO DIP-100 digital polarimeter with a sodium lamp as a light source. Number- and weight-average molecular weights (M_n and M_w) of polymers were determined by gel permeation chromatography (GPC) on TSK gel α -M and TSK gel GMH_{XL}, using a solution of LiBr (10 mM) in *N,N*-dimethylformamide (DMF) as an eluent at a flow rate of 1.0 mL/min, calibrated by polystyrene standards at 40 °C.

Materials. All reagents for monomer synthesis were used as purchased without purification. 4-Iodo-L-phenylalanine was prepared from phenylalanine as described in the literature.²⁰ DMF used for polymerization was distilled over calcium hydride. $(\text{nbd})\text{Rh}^+[\eta^6\text{-C}_6\text{H}_5\text{B}^-(\text{C}_6\text{H}_5)_3]$ was prepared by the reaction of $[(\text{nbd})\text{RhCl}]_2$ with $\text{NaB}(\text{C}_6\text{H}_5)_4$ as described in the literature.²¹

Monomer Synthesis. *N*-tert-Butoxycarbonyl-4-iodo-L-phenylalanine (2). Triethylamine (7.00 mL, 50.3 mmol) was added to a solution of 4-iodo-L-phenylalanine (5.96 g, 20.5 mmol) in H_2O /dioxane (30 mL/30 mL) at 0 °C. Then, di-*tert*-butyl dicarbonate (5.74 g, 26.3 mmol) was added to the solution, and the resulting solution was stirred at room temperature overnight. H_2O (30 mL) was added and the mixture was washed with ethyl acetate. The aqueous layer was acidified to pH 2 with 2 M HCl, then **2** was extracted from the mixture with ethyl acetate twice. The organic layer was washed with saturated NaCl aq. and dried over anhydrous MgSO_4 . It was concentrated on a rotary evaporator to obtain **2** as a pale brown viscous liquid in 37% yield. ^1H NMR (400 MHz, CDCl_3): δ 1.41 [s, 9H, $(\text{CH}_3)_3\text{C}$ –], 2.94–3.21 [m, 2H, $-\text{CH}_2\text{Ar}$], 4.97–5.08 [m, 1H, $>\text{CHCH}_2$ –], 6.93 [d, J = 7.6 Hz, 2H, Ar], 7.62 [d, J = 8.0 Hz, 2H, Ar], 8.23 [s, 1H, $-\text{NH}$ –]. ^{13}C NMR (100 MHz, CDCl_3): δ 28.23 [$(\text{CH}_3)_3\text{C}$ –], 37.36 [$-\text{CH}_2\text{Ar}$], 60.48 [$>\text{CHCH}_2$ –], 80.36

[(CH₃)₃C–], 92.53 [>CHI], 131.40 [Ar], 135.58 [Ar], 137.56 [Ar], 155.24 [–NHCOO–], 176.93 [–COOH].

***N*-tert-Butoxycarbonyl-4-iodo-L-phenylalanylglycine methyl ester (3a).**

Triethylamine (4 mL, 28.8 mmol) was added to a dispersion of glycine methyl ester hydrochloride (3.18 g, 25.3 mmol) in ethyl acetate (150 mL) at 0 °C. Compound **2** (3.74 g, 9.55 mmol) and 4-[4,6-dimethoxy-1,3,5-triazin-2-yl]-4-methylmorpholinium chloride (TRIAZIMOH, Tokuyama Co., 9.00 g, 27.6 mmol) were added to the mixture, and the resulting mixture was stirred at room temperature overnight. It was washed with 0.5 M HCl, saturated NaHCO₃ aq. NaHCO₃, and saturated NaCl aq. The organic layer was dried over anhydrous MgSO₄ and concentrated on a rotary evaporator. The residual mass was purified by recrystallization from ethyl acetate/hexane to obtain **3a** as a colorless solid in 88% yield. ¹H NMR (400 MHz, CDCl₃): δ 1.45 [s, 9H, (CH₃)₃C–], 3.01–3.13 [m, 2H, –CH₂Ar], 3.72 [s, 3H, –COOCH₃], 3.74–4.15 [m, 2H, –NHCH₂COO–], 4.83–4.88 [m, 1H, –CONHCH₂–], 5.13 [s, 1H, >CHCH₂–], 6.64 [s, 1H, –COONH–], 6.85 [d, *J* = 8.0 Hz, 2H, Ar], 7.60 [d, *J* = 8.0 Hz, 2H, Ar]. ¹³C NMR (100 MHz, CDCl₃): δ 28.23 [(CH₃)₃C–], 37.33 [–CH₂Ar], 44.28 [–NHCH₂COO–], 52.44 [–COOCH₃], 60.36 [>CHCH₂–], 80.36 [(CH₃)₃C–], 92.67 [>CHI], 131.23 [Ar], 135.29 [Ar], 137.64 [Ar], 155.96 [–NHCOO–], 169.14 [–CHCONH–], 171.40 [–CH₂COO–].

***N*-tert-Butoxycarbonyl-4-iodo-L-phenylalanyl-L-leucine methyl ester (3b).**

The title compound was synthesized from L-leucine methyl ester hydrochloride and **2** in a manner similar to **3a**. Yield 37%. ¹H NMR (400 MHz, CDCl₃): δ 0.91 [d, 6H, 4.0 Hz, –CH(CH₃)₂], 1.41 [s, 9H, (CH₃)₃C–], 1.46–1.61 [m, 3H, –CH(CH₃)₂ and –CH₂CH(CH₃)₂], 2.92–3.06 [m, 2H, –CH₂Ar], 3.71 [s, 3H, –COOCH₃], 4.34 [s, 1H, –CONHCH₂–], 4.50–4.61 [m, 1H, >CHCH₂CH(CH₃)₂], 5.05–5.13 [m, 1H, >CHCH₂Ar], 6.41 [d, 1H, *J* = 7.8 Hz, –COONH–], 6.96 [d, *J* = 8.0 Hz, 2H, Ar], 7.61

[d, $J = 8.0$ Hz, 2H, Ar]. ^{13}C NMR (100 MHz, CDCl_3): δ 21.79 and 22.69 [$-\text{CH}(\text{CH}_3)_2$], 24.60 [$-\text{CH}(\text{CH}_3)_2$], 28.17 [$(\text{CH}_3)_3\text{C}-$], 37.55 [$-\text{CH}_2\text{Ar}$], 41.42 [$-\text{CH}_2\text{CH}(\text{CH}_3)_2$], 50.67 [$>\text{CHCH}_2\text{CH}(\text{CH}_3)_2$], 52.30 [$-\text{COOCH}_3$], 55.84 [$>\text{CHCH}_2\text{Ar}$], 80.25 [$(\text{CH}_3)_3\text{C}-$], 92.27 [$>\text{CHI}$], 131.38 [Ar], 136.22 [Ar], 137.53 [Ar], 155.27 [$-\text{NHCOO}-$], 170.63 [$-\text{CHCONH}-$], 172.76 [$-\text{CH}_2\text{COO}-$].

N-tert-Butoxycarbonyl-4-iodo-L-phenylalanyl-O-cyclohexyl-L-glutamic acid methyl ester (3c). The title compound was synthesized from *O*-cyclohexyl-L-glutamic acid methyl ester trifluoroacetate and **2** in a manner similar to **3a**. Yield 44%. ^1H NMR (400 MHz, CDCl_3): δ 1.40 [s, 9H, $(\text{CH}_3)_3\text{C}-$], 1.33–1.82 [m, 10H, $-\text{OCH}(\text{CH}_2)_5$], 1.91–2.18 [m, 2H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 2.25–2.40 [m, 2H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 2.91–3.08 [m, 2H, $-\text{CH}_2\text{Ar}$], 3.72 [s, 3H, $-\text{COOCH}_3$], 4.37 [s, 1H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 4.54–4.65 [m, 1H, $-\text{NH}-$], 4.70–4.80 [m, 1H, $-\text{OCH}(\text{CH}_2)_5$], 5.19 [s, 1H, $>\text{CHCH}_2\text{Ar}$], 6.96 [d, $J = 8.3$ Hz, 2H, Ar], 7.59 [d, $J = 8.3$ Hz, 2H, Ar]. ^{13}C NMR (100 MHz, CDCl_3): δ 23.57, 25.16, 27.13, 30.27, and 31.41 [$-\text{OCH}(\text{CH}_2)_5$ and $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 28.10 [$(\text{CH}_3)_3\text{C}-$], 37.52 [$-\text{CH}_2\text{Ar}$], 52.35 [$-\text{COOCH}_3$], 55.17 [$>\text{CHCH}_2\text{Ar}$], 60.22 [$>\text{CHCH}_2\text{CH}_2\text{COO}-$], 72.92 [$-\text{OCH}(\text{CH}_2)_5$], 80.05 [$(\text{CH}_3)_3\text{C}-$], 92.20 [$>\text{CHI}$], 131.30 [Ar], 136.10 [Ar], 137.41 [Ar], 155.15 [$-\text{NHCOO}-$], 170.90 [$-\text{CHCONH}-$], 171.61 [$-\text{COOCH}(\text{CH}_2)_5$], 171.89 [$-\text{COOCH}_3$].

N-tert-Butoxycarbonyl-4-iodo-L-phenylalanyl-O-n-octyl-L-glutamic acid methyl ester (3d). The title compound was synthesized from *O*-*n*-octyl-L-glutamic acid methyl ester trifluoroacetate and **2** in a manner similar to **3a**. Yield 45%. ^1H NMR (400 MHz, CDCl_3): δ 0.88 [t, 3H, $J = 6.8$ Hz, $-\text{COO}(\text{CH}_2)_7\text{CH}_3$], 1.24–1.36 [m, 10H, $-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 1.41 [s, 9H, $(\text{CH}_3)_3\text{C}-$], 1.54–1.69 [m, 2H, $-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 1.89–2.22 [m, 2H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 2.22–2.45 [m, 2H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 2.92–3.12 [m, 2H, $-\text{CH}_2\text{Ar}$], 3.73 [s, 3H, $-\text{COOCH}_3$], 4.05 [t, 2H, $J = 6.6$ Hz, $-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 4.35 [s, 1H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$],

4.53–4.64 [m, 1H, –NH–], 5.01–5.14 [m, 1H, >CHCH₂Ar], 6.68–6.78 [m, 1H, –NH–], 6.96 [d, *J* = 8.1 Hz, 2H, Ar], 7.60 [d, *J* = 8.3 Hz, 2H, Ar]. ¹³C NMR (100 MHz, CDCl₃): δ 14.00 [–COOCH₂CH₂(CH₂)₅CH₃], 22.54, 25.81, 27.19, 28.50, 29.13, and 31.69 [–COOCH₂CH₂(CH₂)₅CH₃ and >CHCH₂CH₂COO–], 28.15 [(CH₃)₃C–], 37.59 [–CH₂Ar], 52.52 [–COOCH₃], 55.34 [>CHCH₂Ar], 60.31 [>CHCH₂CH₂COO–], 64.91 [–COOCH₂CH₂(CH₂)₅CH₃], 80.24 [(CH₃)₃C–], 92.31 [>CHI], 131.35 [Ar], 136.11 [Ar], 137.55 [Ar], 155.18 [–NHCOO–], 170.82 [–CHCONH–], 171.60 [–COOCH(CH₂)₅], 172.68 [–COOCH₃].

cyclo(4-Iodo-L-phenylalanyl-glyciny) (4a). Trifluoroacetic acid (TFA, 2.5 mL, 33.7 mmol) was added to a solution of **3a** (3.90 g, 8.43 mmol) in CH₂Cl₂ (50 mL) at 0 °C overnight. The resulting solution was concentrated in vacuo to obtain 4-iodo-L-phenylalanyl glycine methyl ester trifluoroacetate. It was dissolved in mesitylene (200 mL), and then triethylamine (20 mL) was added to the solution. The reaction mixture was refluxed for 6 h, and a mass precipitated was separated by filtration. It was washed with H₂O to obtain **4a** as a white solid in 27% yield. ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.77–3.12 [m, 2H, –CH₂Ar], 3.38–3.58 [m, 2H, –NHCH₂CO–], 3.96–4.15 [m, 1H, >CHCH₂–], 6.99 [d, *J* = 7.6 Hz, 2H, Ar], 7.62 [d, *J* = 7.6 Hz, 2H, Ar], 7.80 [s, 1H, –NH–], 8.02 [s, 1H, –NH–]. ¹³C NMR (100 MHz, DMSO-*d*₆): δ 37.96 [–CH₂Ar], 43.76 [–NHCH₂CO–], 55.10 [>CHCH₂Ar], 92.35 [>CHI], 132.19 [Ar], 135.90 [Ar], 136.73 [Ar], 165.50 [C=O], 166.83 [C=O].

cyclo(4-Iodo-L-phenylalanyl-L-leuciny) (4b). The title compound was synthesized from **3b** in a manner similar to **4a**. Yield 28%. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.68 [d, 6H, *J* = 6.6 Hz, –CH(CH₃)₂], 0.28–0.38 and 0.80–0.92 [m, 2H, –CH₂CH(CH₃)₂], 1.38–1.51 [m, 1H, –CH(CH₃)₂], 2.78–3.10 [m, 2H, –CH₂Ar], 3.51 [s, 1H, >CHCH₂CH(CH₃)₂], 4.15 [s, 1H, >CHCH₂Ar], 6.95 [d, *J* = 8.0 Hz, 2H, Ar], 7.62 [d, *J* = 8.1 Hz, 2H, Ar], 7.95 [s, 1H, –NH–], 7.97 [s, 1H, –NH–]. ¹³C NMR (100

MHz, DMSO- d_6): δ 21.50 [$-\text{CH}(\text{CH}_3)_2$], 22.92 [$-\text{CH}(\text{CH}_3)_2$], 37.75 [$-\text{CH}_2\text{Ar}$], 43.50 [$-\text{CH}_2\text{CH}(\text{CH}_3)_2$], 52.27 [$>\text{CHCH}_2\text{CH}(\text{CH}_3)_2$], 57.40 [$>\text{CHCH}_2\text{Ar}$], 92.54 [$>\text{CHI}$], 132.50 [Ar], 135.73 [Ar], 136.66 [Ar], 165.75 [C=O], 167.23 [C=O].

cyclo(4-Iodo-L-phenylalanyl-O-cyclohexyl-L-glutaminy) (4c). The title compound was synthesized from **3c** in a manner similar to **4a**. Yield 70%. ^1H NMR (400 MHz, DMSO- d_6): δ 1.24–1.88 [m, 14H, $-\text{COOCH}(\text{CH}_2)_5$, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 2.78–3.13 [m, 2H, $-\text{CH}_2\text{Ar}$], 3.70–3.84 [m, 1H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 4.11–4.22 [m, 1H, $>\text{CHCH}_2\text{Ar}$], 4.56–4.70 [m, 1H, $-\text{COOCH}(\text{CH}_2)_5$], 6.97 [d, $J = 7.8$ Hz, 2H, Ar], 7.60 [d, $J = 8.0$ Hz, 2H, Ar], 7.99 [s, 1H, $-\text{NH}-$], 8.08 [s, 1H, $-\text{NH}-$]. ^{13}C NMR (100 MHz, DMSO- d_6): δ 23.01, 24.71, 25.50, 28.83, and 30.94 [$-\text{COOCH}(\text{CH}_2)_5$ and $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 37.30 [$-\text{CH}_2\text{Ar}$], 52.80 [$>\text{CHCH}_2\text{CH}_2\text{COO}-$], 54.87 [$>\text{CHCH}_2\text{Ar}$], 71.73 [$-\text{COOCH}(\text{CH}_2)_5$], 92.23 [$>\text{CHI}$], 132.39 [Ar], 135.80 [Ar], 136.63 [Ar], 166.06 [C=O], 166.42 [C=O], 171.26 [$-\text{COO}-$].

cyclo(4-Iodo-L-phenylalanyl-O-n-octyl-L-glutaminy) (4d). The title compound was synthesized from **3d** in a manner similar to **4a**. Yield 65%. ^1H NMR (400 MHz, DMSO- d_6): δ 0.86 [t, 3H, $J = 6.8$ Hz, $-\text{COO}(\text{CH}_2)_7\text{CH}_3$], 1.21–1.50 [m, 12H, $-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 1.50–1.69 [m, 2H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 1.69–2.01 [m, 2H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 2.76–3.13 [m, 2H, $-\text{CH}_2\text{Ar}$], 3.71–3.83 [m, 1H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 3.91–4.08 [m, 2H, $-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 4.13–4.34 [m, 1H, $>\text{CHCH}_2\text{Ar}$], 6.97 [d, $J = 8.0$ Hz, 2H, Ar], 7.60 [d, $J = 8.0$ Hz, 2H, Ar], 7.99 [s, 1H, $-\text{NH}-$], 8.08 [s, 1H, $-\text{NH}-$]. ^{13}C NMR (100 MHz, DMSO- d_6): δ 13.62 [$-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 21.79, 25.15, 27.96, 28.31, and 30.94 [$-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$ and $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 37.50 [$-\text{CH}_2\text{Ar}$], 52.84 [$>\text{CHCH}_2\text{CH}_2\text{COO}-$], 54.85 [$>\text{CHCH}_2\text{Ar}$], 63.67 [$-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 92.31 [$>\text{CHI}$], 132.36 [Ar], 135.77 [Ar], 136.59 [Ar], 166.01 [C=O], 166.33 [C=O], 171.85

[–COO–].

cyclo(4-Trimethylsilylethynyl-L-phenylalanyl-glyciny)l (5a). Compound **4a** (762 mg, 2.31 mmol), PdCl₂(PPh₃)₂ (12.5 mg, 17.8 μmol), PPh₃ (19.9 mg, 75.9 μmol), and CuI (23.0 mg, 121 μmol) were added into a two-neck flask and it was flushed with hydrogen. DMF (12 mL) and triethylamine (2 mL) were added to the flask and then (trimethylsilyl)acetylene (1.5 mL) was added dropwise to the solution and the yellow mixture was stirred at room temperature overnight. The resulting mixture was concentrated in vacuo and the residual mass was washed with 0.5 M HCl and hexane to obtain **5a** in 65% yield. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.22 [s, 9H, (CH₃)₃Si–], 2.49–2.94 [m, 2H, –CH₂Ar], 3.40–3.45 [m, 2H, –NHCH₂CO–], 4.07 [s, 1H, –NHCHCO–], 7.18 [d, 2H, *J* = 8.3 Hz, Ar], 7.35 [d, 2H, *J* = 8.1 Hz, Ar], 7.79 [s, 1H, –NH–], 8.02 [s, 1H, –NH–]. ¹³C NMR (100 MHz, DMSO-*d*₆): δ –0.36 [(CH₃)₃Si–], 38.40 [–CH₂Ar], 43.65 [–NHCH₂CO–], 55.10 [–NHCHCO–], 93.92 [–C≡CSi(CH₃)₃], 105.01 [–C≡CSi(CH₃)₃], 120.46 [Ar], 130.07 [Ar], 131.13 [Ar], 137.17 [Ar], 165.34 [C=O], 166.73 [C=O].

cyclo(4-Trimethylsilylethynyl-L-phenylalanyl-L-leuciny)l (5b). The title compound was synthesized from **4b** in a manner similar to **5a**. Yield 63%. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.19 [s, 9H, (CH₃)₃Si–], 0.66 [s, 6H, *J* = 7.2 Hz, –CH(CH₃)₂], 1.19 [t, 2H, *J* = 7.3 Hz, –CH₂CH(CH₃)₂], 1.36–1.53 [m, 1H, –CH(CH₃)₂], 3.04–3.17 [m, 2H, –CH₂Ar], 3.50 [s, 1H, >CHCH₂CH(CH₃)₂], 4.16 [s, 1H, >CHCH₂Ar], 7.13 [d, *J* = 7.8 Hz, 2H, Ar], 7.34 [d, *J* = 7.8 Hz, 2H, Ar], 7.94 [s, 1H, –NH–], 7.96 [s, 1H, –NH–]. ¹³C NMR (100 MHz, DMSO-*d*₆): δ –0.20 [(CH₃)₃Si–], 21.31 [–CH(CH₃)₂], 22.95 [–CH(CH₃)₂], 38.23 [–CH₂Ar], 43.55 [–CH₂CH(CH₃)₂], 52.28 [>CHCH₂CH(CH₃)₂], 55.39 [>CHCH₂Ar], 93.82 [–C≡CSi(CH₃)₃], 105.09 [–C≡CSi(CH₃)₃], 120.74 [Ar], 130.45 [Ar], 131.16 [Ar], 137.11 [Ar], 165.88 [C=O], 167.33 [C=O].

cyclo(4-Trimethylsilylethynyl-L-phenylalanyl-O-cyclohexyl-L-glutaminyl)

(5c). The title compound was synthesized from **4c** in a manner similar to **5a**. Yield 56%. ^1H NMR (400 MHz, DMSO- d_6): δ 0.20 [s, 9H, $(\text{CH}_3)_3\text{Si}$ –], 1.19–1.86 [m, 14H, $-\text{COOCH}(\text{CH}_2)_5$, $>\text{CHCH}_2\text{CH}_2\text{COO}$ –], 2.79–3.17 [m, 2H, $-\text{CH}_2\text{Ar}$], 3.70–3.81 [m, 1H, $>\text{CHCH}_2\text{CH}_2\text{COO}$ –], 4.16–4.27 [m, 1H, $>\text{CHCH}_2\text{Ar}$], 4.54–4.66 [m, 1H, $-\text{COOCH}(\text{CH}_2)_5$], 7.16 [d, $J = 7.8$ Hz, 2H, Ar], 7.32 [d, $J = 8.1$ Hz, 2H, Ar], 7.99 [s, 1H, $-\text{NH}$ –], 8.09 [s, 1H, $-\text{NH}$ –]. ^{13}C NMR (100 MHz, DMSO- d_6): δ –0.26 [$(\text{CH}_3)_3\text{Si}$ –], 23.01, 24.72, 28.45, 28.73, and 30.88 [$-\text{COOCH}(\text{CH}_2)_5$ and $>\text{CHCH}_2\text{CH}_2\text{COO}$ –], 37.64 [$-\text{CH}_2\text{Ar}$], 52.94 [$>\text{CHCH}_2\text{CH}_2\text{COO}$ –], 54.93 [$>\text{CHCH}_2\text{Ar}$], 71.52 [$-\text{COOCH}(\text{CH}_2)_5$], 93.70 [$-\text{C}\equiv\text{CSi}(\text{CH}_3)_3$], 105.09 [$-\text{C}\equiv\text{CSi}(\text{CH}_3)_3$], 120.62 [Ar], 130.35 [Ar], 131.08 [Ar], 137.15 [Ar], 166.08 [C=O], 166.43 [C=O], 171.25 [$-\text{COO}$ –].

***cyclo(4-Trimethylsilylethynyl-L-phenylalanyl-O-n-octyl-L-glutaminyl)* (5d).**

The title compound was synthesized from **4d** in a manner similar to **5a**. Yield 62%. ^1H NMR (400 MHz, DMSO- d_6): δ 0.20 [s, 9H, $(\text{CH}_3)_3\text{Si}$ –], 0.86 [t, 3H, $J = 6.7$ Hz, $-\text{COO}(\text{CH}_2)_7\text{CH}_3$], 1.20–1.36 [m, 10H, $-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 1.36–1.48 [m, 2H, $-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 1.48–1.64 [m, 2H, $>\text{CHCH}_2\text{CH}_2\text{COO}$ –], 1.64–1.84 [m, 2H, $>\text{CHCH}_2\text{CH}_2\text{COO}$ –], 2.76–3.17 [m, 2H, $-\text{CH}_2\text{Ar}$], 3.70–3.76 [m, 1H, $>\text{CHCH}_2\text{CH}_2\text{COO}$ –], 3.96 [t, $J = 6.6$ Hz, 2H, $-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 4.16–4.23 [m, 1H, $>\text{CHCH}_2\text{Ar}$], 7.16 [d, $J = 7.8$ Hz, 2H, Ar], 7.32 [d, $J = 8.0$ Hz, 2H, Ar], 7.99 [s, 1H, $-\text{NH}$ –], 8.09 [s, 1H, $-\text{NH}$ –]. ^{13}C NMR (100 MHz, DMSO- d_6): δ 0.00 [$(\text{CH}_3)_3\text{Si}$ –], 13.92 [$-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 21.08, 25.48, 28.26, 28.68, and 31.24 [$-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$ and $>\text{CHCH}_2\text{CH}_2\text{COO}$ –], 37.94 [$-\text{CH}_2\text{Ar}$], 53.18 [$>\text{CHCH}_2\text{CH}_2\text{COO}$ –], 55.22 [$>\text{CHCH}_2\text{Ar}$], 63.83 [$-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 91.70 [$-\text{C}\equiv\text{CSi}(\text{CH}_3)_3$], 105.38 [$-\text{C}\equiv\text{CSi}(\text{CH}_3)_3$], 120.91 [Ar], 130.59 [Ar], 131.33 [Ar], 137.42 [Ar], 166.30 [C=O], 166.65 [C=O], 172.13 [$-\text{COO}$ –].

cyclo(4-Ethynyl-L-phenylalanyl-glyciny) (1a). 1 M Tetrabutylammonium fluoride solution in THF (1.0 mL) was added dropwise to a solution of **5a** (449 mg, 1.49 mmol) in DMF (12 mL) and the solution was stirred for 20 minutes. The resulting solution was concentrated in vacuo and the residual mass was washed with 0.5 M HCl and ethyl acetate to obtain **1a** in 43% yield. No mp was observed below 270 °C. $[\alpha]_D -2^\circ$ ($c = 0.10$ g/dL in DMF at room temperature). ^1H NMR (400 MHz, DMSO- d_6): δ 2.91–3.12 [m, 2H, $-\text{CH}_2\text{Ar}$], 3.42–3.47 [m, 2H, $-\text{NHCH}_2\text{CO}-$], 4.05 [s, 1H, $-\text{C}\equiv\text{CH}$], 4.07 [m, 1H, $-\text{NHCHCO}-$], 7.19 [d, 2H, $J = 8.0$ Hz, Ar], 7.38 [d, 2H, $J = 8.0$ Hz, Ar], 7.80 [s, 1H, $-\text{NH}-$], 8.03 [s, 1H, $-\text{NH}-$]. ^{13}C NMR (100 MHz, DMSO- d_6): δ 38.33 [$-\text{CH}_2\text{Ar}$], 43.65 [$-\text{NHCH}_2\text{CO}-$], 55.29 [$-\text{NHCHCO}-$], 77.75 [$-\text{C}\equiv\text{CH}$], 83.27 [$-\text{C}\equiv\text{CH}$], 129.94 [Ar], 129.99 [Ar], 131.22 [Ar], 137.17 [Ar], 165.37 [C=O], 166.75 [C=O]. IR (cm^{-1} , KBr): 3579, 3464, 3251 (NH), 3197 (NH), 3049, 2977 (CH), 2926 (CH), 2878 (CH), 2106 ($\text{C}\equiv\text{C}$), 1924(Ar), 1678 (NHCO), 1505, 1467, 1333, 822. HRMS. Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2$ (m/z) 228.0899. Found: 228.0900.

cyclo(4-Ethynyl-L-phenylalanyl-L-leuciny) (1b). The title compound was synthesized from **5b** in a manner similar to **1a**. Yield 40%. Mp 229–232 °C. $[\alpha]_D -34^\circ$ ($c = 0.10$ g/dL in DMF at room temperature). ^1H NMR (400 MHz, DMSO- d_6): δ 0.66 [t, 6H, $J = 6.1$ Hz, $-\text{CH}(\text{CH}_3)_2$], 1.17 [t, 2H, $J = 7.1$ Hz, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$], 1.38–1.52 [m, 1H, $-\text{CH}(\text{CH}_3)_2$], 2.85–3.15 [m, 2H, $-\text{CH}_2\text{Ar}$], 3.51 [s, 1H, $>\text{CHCH}_2\text{CH}(\text{CH}_3)_2$], 4.00 [s, 1H, $-\text{C}\equiv\text{CH}$], 4.17 [s, 1H, $>\text{CHCH}_2\text{Ar}$], 7.15 [d, $J = 8.0$ Hz, 2H, Ar], 7.37 [d, $J = 7.8$ Hz, 2H, Ar], 7.95 [s, 1H, $-\text{NH}-$], 7.97 [s, 1H, $-\text{NH}-$]. ^{13}C NMR (100 MHz, DMSO- d_6): δ 20.51 [$-\text{CH}(\text{CH}_3)_2$], 22.86 [$-\text{CH}(\text{CH}_3)_2$], 38.87 [$-\text{CH}_2\text{Ar}$], 43.44 [$-\text{CH}_2\text{CH}(\text{CH}_3)_2$], 52.10 [$>\text{CHCH}_2\text{CH}(\text{CH}_3)_2$], 59.47 [$>\text{CHCH}_2\text{Ar}$], 80.27 [$-\text{C}\equiv\text{CH}$], 83.09 [$-\text{C}\equiv\text{CH}$], 120.15 [Ar], 130.41 [Ar], 131.21 [Ar], 137.07 [Ar], 165.85 [C=O], 167.26 [C=O]. IR (cm^{-1} , KBr): 3302 (NH), 3198 (NH), 3049 (Ar), 2959 (CH), 2927 (CH), 2897 (CH), 2109 ($\text{C}\equiv\text{C}$), 1924(Ar), 1663 (NHCO), 1505, 1460,

1330, 1117, 826. HRMS. Calcd for $C_{17}H_{20}N_2O_2$ (m/z) 284.1525. Found: 284.1526.

cyclo(4-Ethynyl-L-phenylalanyl-O-cyclohexyl-L-glutaminy) (1c). The title compound was synthesized from **5c** in a manner similar to **1a**. Yield 18%. Mp 196–200 °C. $[\alpha]_D -34^\circ$ ($c = 0.10$ g/dL in DMF at room temperature). 1H NMR (400 MHz, DMSO- d_6): δ 1.22–1.90 [m, 14H, $-\text{COOCH}(\text{CH}_2)_5$, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 2.83–3.19 [m, 2H, $-\text{CH}_2\text{Ar}$], 3.55–3.70 [m, 1H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 3.99 [s, 1H, $-\text{C}\equiv\text{CH}$], 4.12–4.28 [m, 1H, $>\text{CHCH}_2\text{Ar}$], 4.53–4.67 [m, 1H, $-\text{COOCH}(\text{CH}_2)_5$], 7.19 [d, $J = 7.8$ Hz, 2H, Ar], 7.35 [d, $J = 8.1$ Hz, 2H, Ar], 7.99 [s, 1H, $-\text{NH}-$], 8.09 [s, 1H, $-\text{NH}-$]. ^{13}C NMR (100 MHz, DMSO- d_6): δ 23.02, 24.70, 28.48, 28.81, 29.11, and 30.85 [$-\text{COOCH}(\text{CH}_2)_5$ and $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 37.65 [$-\text{CH}_2\text{Ar}$], 53.10 [$>\text{CHCH}_2\text{CH}_2\text{COO}-$], 54.86 [$>\text{CHCH}_2\text{Ar}$], 71.70 [$-\text{COOCH}(\text{CH}_2)_5$], 79.78 [$-\text{C}\equiv\text{CH}$], 83.23 [$-\text{C}\equiv\text{CH}$], 120.11 [Ar], 130.33 [Ar], 131.13 [Ar], 137.06 [Ar], 166.05 [C=O], 166.98 [C=O], 171.24 [$-\text{COO}-$]. IR (cm^{-1} , KBr): 3270 (NH), 3234 (NH), 3192 (NH), 3051 (Ar), 2936 (CH), 2858 (CH), 2109 ($\text{C}\equiv\text{C}$), 1926 (Ar), 1732 (C=O), 1671 (NHCO), 1458, 1335, 1252, 1169, 825. HRMS. Calcd for $C_{22}H_{26}N_2O_4$ (m/z) 382.1891. Found: 382.1893.

cyclo(4-Ethynyl-L-phenylalanyl-O-n-octyl-L-glutaminy) (1d). The title compound was synthesized from **5d** in a manner similar to **1a**. Yield 70%. Mp 176–177 °C. $[\alpha]_D -3^\circ$ ($c = 0.10$ g/dL in DMF at room temperature). 1H NMR (400 MHz, DMSO- d_6): δ 0.87 [t, 3H, $J = 6.6$ Hz, $-\text{COO}(\text{CH}_2)_7\text{CH}_3$], 1.21–1.37 [m, 10H, $-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 1.37–1.50 [m, 2H, $-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 1.50–1.62 [m, 2H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 1.71–1.88 [m, 2H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 2.83–3.17 [m, 2H, $-\text{CH}_2\text{Ar}$], 3.71–3.77 [m, 1H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 3.96 [t, $J = 6.6$ Hz, 2H, $-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 3.98 [s, 1H, $-\text{C}\equiv\text{CH}$], 4.16–4.23 [m, 1H, $>\text{CHCH}_2\text{Ar}$], 7.18 [d, $J = 8.1$ Hz, 2H, Ar], 7.35 [d, $J = 8.0$ Hz, 2H, Ar], 7.99 [s, 1H, $-\text{NH}-$], 8.09 [s,

^1H , $-\text{NH}-$]. ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 13.69 [$-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 21.86, 25.21, 27.98, 28.39, 28.43, and 31.01 [$-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$ and $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 37.76 [$-\text{CH}_2\text{Ar}$], 52.93 [$>\text{CHCH}_2\text{CH}_2\text{COO}-$], 55.01 [$>\text{CHCH}_2\text{Ar}$], 63.70 [$-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 79.86 [$-\text{C}\equiv\text{CH}$], 83.26 [$-\text{C}\equiv\text{CH}$], 120.21 [Ar], 130.35 [Ar], 131.19 [Ar], 137.09 [Ar], 166.13 [$\text{C}=\text{O}$], 166.16 [$\text{C}=\text{O}$], 171.94 [$-\text{COO}-$]. IR (cm^{-1} , KBr): 3306 (NH), 3263 (NH), 3192 (NH), 3050 (Ar), 2957 (CH), 2925 (CH), 2856 (CH), 2111 ($\text{C}\equiv\text{C}$), 1925 (Ar), 1734 ($\text{C}=\text{O}$), 1686 (NHCO), 1672 (NHCO), 1460, 1337, 1250, 1170, 1110, 825. HRMS. Calcd for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_4$ (m/z) 412.2362. Found: 412.2363.

Polymerization. The polymerization was carried out in a glass tube equipped with a three-way stopcock under nitrogen. $(\text{nbd})\text{Rh}^+[\eta^6\text{-C}_6\text{H}_5\text{B}^-(\text{C}_6\text{H}_5)_3]$ (2.1 mg, 5 μmol) was added to a solution of a monomer (0.20 mmol) in DMF (1.0 mL), and the resulting mixture was vigorously stirred. It was kept in a water bath at 30 $^\circ\text{C}$ for 24 h. The resulting mixture was poured into MeOH (50 mL) to precipitate a polymer. It was separated by filtration using a membrane filter (ADVANTEC H100A047A), and dried under reduced pressure.

Spectroscopic Data of the Polymers. **Poly(1a);** IR (cm^{-1} , KBr): 3368, 3230 (NH), 2962 (CH), 2919 (CH), 2854 (CH), 1925 (Ar), 1670 (NHCO), 1458, 1325. **Poly(1b);** IR (cm^{-1} , KBr): 3213 (NH), 3084 (NH), 2956 (CH), 2870 (CH), 1911(Ar), 1671 (NHCO), 1459, 1318. **Poly(1c);** ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 0.88–1.94 [br, 12H, $-\text{COOCH}(\text{CH}_2)_5$, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 2.06–2.39 [br, 2H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 3.68–3.95 [br, 1H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 3.95–4.38 [br, 2H, $>\text{CHCH}_2\text{Ar}$], 4.47–4.76 [br, 1H, $-\text{COOCH}(\text{CH}_2)_5$], 5.46–6.00 [br, 1H, $-\text{CH}=\text{C}<$], 6.18–7.35 [br, 4H, Ar], 7.57–7.88 [br, 1H, $-\text{NH}-$], 7.88–8.33 [br, 1H, $-\text{NH}-$]. IR (cm^{-1} , KBr): 3230 (NH), 2932 (CH), 2858 (CH), 1919 (Ar), 1725 ($\text{C}=\text{O}$), 1675 (NHCO), 1450, 1329, 1254, 1174. **Poly(1d);** ^1H NMR (400 MHz, $\text{DMF}-d_7$): δ 0.86

[s, 3H, $-\text{COO}(\text{CH}_2)_7\text{CH}_3$], 1.26 [s, 10H, $-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$], 1.56 [s, 2H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 2.15–2.62 [br, 2H, $>\text{CHCH}_2\text{CH}_2\text{COO}-$], 3.76–4.58 [br, 3H, $-\text{COOCH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$ and $>\text{CHCH}_2\text{Ar}$], 5.56–6.20 [br, 1H, $-\text{CH}=\text{C}<$], 6.20–7.68 [br, 4H, Ar], 7.68–8.70 [br, 2H, $-\text{NH}-$]. IR (cm^{-1} , KBr): 3231 (NH), 2954 (CH), 2927 (CH), 2855 (CH), 1911(Ar), 1735 (C=O), 1678 (NHCO), 1450, 1330, 1173.

References and Notes

- (1) (a) Martins, M. B.; Carvalho, I. *Tetrahedron* **2007**, *63*, 9923. (b) Peterkofsky, A.; Battaini, F.; Koch, Y.; Takahara, Y.; Dannies, P. *Mol. Cell. Biochem.* **1982**, *42*, 45.
- (2) Du, Y.; Creighton, J. C.; Tounge, B. A.; Reitz, A. B. *Org. Lett.* **2004**, *6*, 309.
- (3) Kloster, R. A.; Selby, H. D.; Miller III, W. B.; Mash, E. A. *J. Org. Chem.* **2005**, *70*, 8693.
- (4) Kloster, R. A.; Carducci, M. D.; Mash, E. A. *Org. Lett.* **2003**, *5*, 3683.
- (5) Bergeron, R. J.; Phanstiel IV, O.; Yao, G. W.; Milstein, S.; Weimar, W. R. *J. Am. Chem. Soc.* **1994**, *116*, 8479.
- (6) Hanabusa, K.; Fukui, H.; Suzuki, M.; Shirai, H. *Langmuir* **2005**, *21*, 10383.
- (7) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910.
- (8) (a) Crescenzi, V.; Giancotti, V.; Quadrifoglio, F. *Makromol. Chem.* **1968**, *120*, 220. (b) Majó, M. A.; Bou, J. J.; Herranz, C.; Muñoz-Guerra, S. *Macromol. Chem. Phys.* **2006**, *207*, 615. (c) Kunisaki, T.; Kawai, K.; Hirohata, K.; Minami, K.; Kondo, K. *J. Polym. Sci. Part A: Polym. Chem.* **2001**, *39*, 927. (d) Akerlund, J.; Harmeier, S.; Pumphrey, J.; Timm, D. C.; Brand, J. I. *J. Appl. Polym. Sci.* **2000**, *78*, 2213.
- (9) Terada, K.; Sanda, F.; Masuda, T. *J. Macromol. Sci., Part A: Pure & Appl. Chem.* **2007**, *44*, 789.
- (10) Terada, K.; Berda, E. B.; Wagener, K. B.; Sanda, F.; Masuda, T. *Macromolecules* **2008**, *41*, 6041.
- (11) (a) Ciardelli, F.; Lanzillo, S.; Pieroni, O. *Macromolecules* **1974**, *7*, 174. (b) Tang, B. Z.; Kotera, N. *Macromolecules* **1989**, *22*, 4388. (c) Yamaguchi, M.; Omata, K.; Hiramata, M. *Chem. Lett.* **1992**, *21*, 2261. (d) Aoki, T.; Kokai, M.; Shinohara, K.; Oikawa, E. *Chem. Lett.* **1993**, *22*, 2009. (e) Yashima, E.; Huang, S.; Okamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994**, *15*, 1811. (f) Yashima, E.; Huang, S.; Matsushima, T.; Okamoto, Y. *Macromolecules* **1995**, *28*, 4184.

- (g) Nakako, H.; Nomura, R.; Tabata, M.; Masuda, T. *Macromolecules* **1999**, *32*, 2861. (h) Nomura, R.; Fukushima, Y.; Nakako, H.; Mauda, T. *J. Am. Chem. Soc.* **2000**, *122*, 8830.
- (12) Tabata, M.; Yang, Y.; Yokota, K. *Polym. J.* **1990**, *22*, 1105.
- (13) Reviews: (a) Yashima, E.; Maeda, K.; Nishimura, T. *Chem. Eur. J.* **2004**, *10*, 42. (b) Lam, J. W. Y.; Tang, B. Z. *Acc. Chem. Res.* **2005**, *38*, 745. (c) Aoki, T.; Kaneko, T.; Teraguchi, M. *Polymer*, **2006**, *47*, 4867. (d) Masuda, T. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 165.
- (14) (a) Nomura, R.; Tabei, J.; Masuda, T. *J. Am. Chem. Soc.* **2001**, *123*, 8430. (b) Tabei, J.; Nomura, R.; Masuda, T. *Macromolecules* **2002**, *35*, 2955. (c) Tabei, J.; Nomura, R.; Masuda, T. *Macromolecules* **2002**, *35*, 5405. (d) Tabei, J.; Nomura, R.; Sanda, F.; Masuda, T. *Macromolecules* **2003**, *36*, 8603.
- (15) (a) Yue, D.; Fujii, T.; Terada, K.; Tabei, J.; Shiotsuki, M.; Sanda, F.; Masuda, T. *Macromol. Rapid Commun.* **2006**, *27*, 1460. (b) Yue, D.; Fujii, T.; Terada, K.; Tabei, J.; Shiotsuki, M.; Sanda, F.; Masuda, T. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 1515.
- (16) Suzuki, Y.; Tabei, J.; Shiotsuki, M.; Inai, Y.; Sanda, F.; Masuda, T. *Macromolecules* **2008**, *41*, 1086.
- (17) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490. The molecular mechanics calculation was carried out with Wavefunction Inc., Spartan '06 Windows.
- (18) Tabei, J.; Shiotsuki, M.; Sanda, F.; Masuda, T. *Macromolecules* **2005**, *38*, 9448.
- (19) (a) Sakurai, S.; Okoshi, K.; Kumaki, J.; Yashima, E. *J. Am. Chem. Soc.* **2006**, *128*, 5650–5651. (b) Sakurai, S.; Okoshi, K.; Kumaki, J.; Yashima, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 1245.
- (20) Lei, H.; Stoakes, M. S.; Herath, K. P. B.; Lee, Jinho.; Schwabacher, A. W. *J. Org. Chem.* **1994**, *59*, 4206.
- (21) Schrock, R. R.; Osborn, J. A. *Inorg. Chem.* **1970**, *9*, 2339.

Chapter 3

Enantioselective Reduction of Aromatic Ketimines with Poly(phenylacetylene)s Taking Helical Structures as Polymer Catalyst

Abstract

Novel optically active ethynyl monomers were synthesized from L-valine and *N*-methyl-L-valine, and polymerized with a rhodium catalyst to obtain the polymers with number-average molecular weights over 200 000 in good yields. The CD and UV-vis spectra of the polymers indicated that they took helical structures with predominantly one-handed screw sense in solution. The polymers served as catalysts of asymmetric reduction of an aromatic ketimine to afford an optically active amine in moderate yields, whose predominant chirality was opposite from that obtained by reduction catalyzed with the corresponding valine- and *N*-methyl valine-derived monomers.

Introduction

Since List and Barbas have reported asymmetric aldol reaction using proline as an organocatalyst in 2000,¹ various proline-catalyzed reactions have been developed, including the Mannich reaction,² α -amination,³ α -aminoxylation,⁴ cross-aldol reaction,⁵ and Michael addition.⁶ They have stimulated asymmetric synthesis utilizing various amino acid derivatives⁷ in addition to proline-derived ones as catalysts.⁸ Besides, it has been also reported that diketopiperazines, cyclic dimers of amino acid, catalyze hydrocyanation enantioselectively⁹ and α -helical polypeptides act as polymeric catalysts in the epoxidation of chalcone.¹⁰

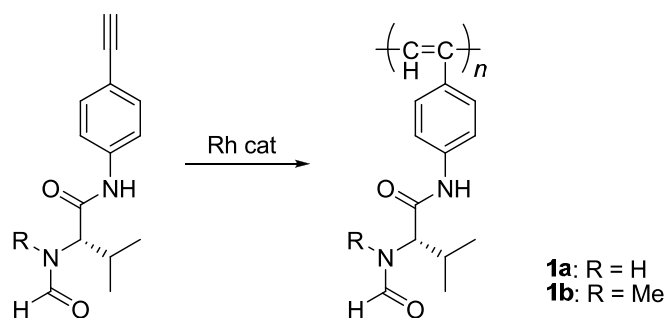
The synthesis of chiral amines is important because they are useful as intermediates for pharmaceutical drugs and agrochemicals. They are currently synthesized by the reduction of imines catalyzed with chiral metal complexes.¹¹ High-pressure hydrogenation,¹² hydrosilylation,¹³ and hydrogen transfer reaction¹⁴ have been also developed, however they have problems such as metal leaching, difficult handling, high cost of metal catalysts, and catalyst regeneration. Stoichiometric borane reduction catalyzed with chiral oxazaborolidines is partly exempt from these problems, and highly enantioselective, but its cost is not suitable for a large-scale industrial process.¹⁵ The combination of Hantzsch dihydropyridine as a stoichiometric reducing agent and a chiral Brønsted acid as an organocatalyst is a recently developed excellent reduction method, but it is still tainted by the cost implications.¹⁶ Trichlorosilane has been recently developed as an inexpensive easy-to-handle agent for a metal-free reduction of ketimines. The reaction is accelerated with a Lewis base such as R_3N , DMF, MeCN, and so on.¹⁷ Matsumura and coworkers have reported the asymmetric reduction of ketimines using formamides derived from L-proline as an activator of trichlorosilane;¹⁸ Malkov and Kočovský have improved the enantioselectivity.¹⁹

Meanwhile, substituted polyacetylenes, well-known conjugated polymers, are synthesized by the polymerization of acetylene derivatives with various transition metal catalysts via insertion or metathesis mechanism.²⁰ Iron-aluminum and rhodium catalysts afford highly *cis*-stereoregular substituted polyacetylenes,²¹ some of which take helical conformations with predominantly one handed screw sense by introducing chiral substituents at the side chains. Ciardelli et al. have reported the first example of substituted helical polyacetylenes in the 1970s. They have synthesized polyacetylenes carrying chiral aliphatic side chains by the polymerization catalyzed with iron tris(acetylacetonate)-triisobutylaluminum, and examined their helical structures in solution.^{21a} Since Tabata et al. have developed [Rh(norbornadiene)Cl]₂-triethylamine as a catalyst for polymerizing monosubstituted acetylenes to obtain *cis*-stereoregular polyacetylenes,²² a wide variety of substituted helical polyacetylenes have been synthesized using the catalyst due to the high tolerance to polar functional groups.^{20d,23} We have reported that poly(*N*-propargylamide)s carrying amino acid residues in the side chains take helical structures stabilized by intramolecular hydrogen bonding between the amide groups, and the helices transform the screw sense responsive to external stimuli such as heat and solvent polarity.²⁴ Tang and coworkers have reported that poly(phenylacetylene)s bearing amino acid residues form helical structures in solution and they assemble into nanostructures such as micelles, vesicles, and globules.²⁵ Yashima and coworkers have synthesized a variety of helical poly(phenylacetylene)s with predominantly one-handed screw sense induced by the interaction with amino acids and peptides.²⁶

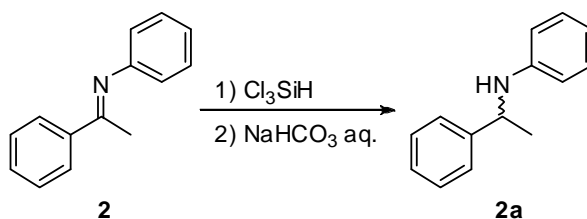
Polymer-supported catalysts are advantageous to recovery compared with common catalysts. So far, several polymer catalysts have been reported, but there are few examples that estimate the catalytic activity regarding the secondary structures.²⁷

It is expected that helical polymer catalysts exhibit unique features based on the active sites regularly arranged at the side chains. The present study deals with the synthesis of amino acid-based poly(phenylacetylene) derivatives (Scheme 1), and asymmetric reduction (hydrosilylation followed by hydrolysis) of an aromatic ketimine in the presence of the polymer to give the corresponding amine (Scheme 2).

Scheme 1



Scheme 2



Results and Discussion

Synthesis and Secondary Structures of the Polymers. Monomers **1a** and **1b** were synthesized from L-valine derivatives (Scheme 3). Table 1 summarizes the conditions and results of the polymerization of **1a** and **1b** catalyzed with $(\text{nbd})\text{Rh}^+[\eta^6\text{-C}_6\text{H}_5\text{B}^-(\text{C}_6\text{H}_5)_3]$ in DMF (Scheme 1). The corresponding polymers with M_n 's of 252 000 and 476 000 were obtained as diethyl ether-insoluble parts in good yields. The initiator efficiency of the rhodium catalyst seems to be low, judging from the molecular weights much higher than those expected from the monomer catalyst

Scheme 3

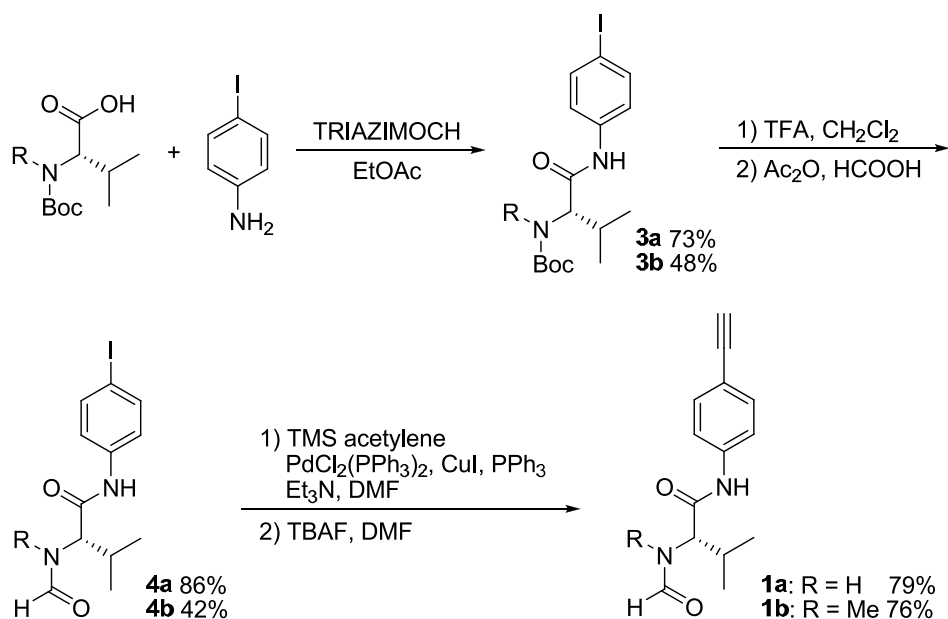


Table 1. Polymerization of **1a and **1b****^a

monomer	polymer				
	$[\alpha]_D^b$	yield ^c	M_n^d	M_w/M_n^d	$[\alpha]_D^b$
	(deg)				
1a	+9	99	252 000	2.42	−604
1b	−90	89	476 000	3.00	−488

^a Catalyst: (nbd)Rh⁺[η^6 -C₆H₅B[−](C₆H₅)₃]; Conditions: [M]₀ = 0.20 M, [M]₀/[Cat] = 100 in DMF at 30 °C for 12 h. ^b Measured by polarimetry at room temperature, *c* = 0.10 g/dL in DMF. ^c Et₂O-insoluble part. ^d Estimated by GPC based on polystyrene standards, eluent; LiBr solution in DMF (10 mM).

ratio (100). Poly(**1a**) was soluble in DMF, while insoluble in MeOH, THF, and CHCl₃. On the other hand, poly(**1b**) was soluble in all these solvents. They were insoluble in toluene. The specific rotations measured in DMF were −609° and −488°, respectively, both of which were much larger than those of the monomers (+9° and

-90°). This strongly suggests that the polymers form a chiral secondary structure such as helix.

Figure 1 depicts the CD and UV-vis spectra of poly(**1a**) and poly(**1b**) measured in various solvents. At 0 °C, both polymers exhibited intense Cotton effects at a UV-absorption area based on the conjugated main chain, indicating that the polymers took helical structures with predominantly one-handed screw sense in the solvent. The helical conformation of poly(**1b**) was thermally stable in THF and

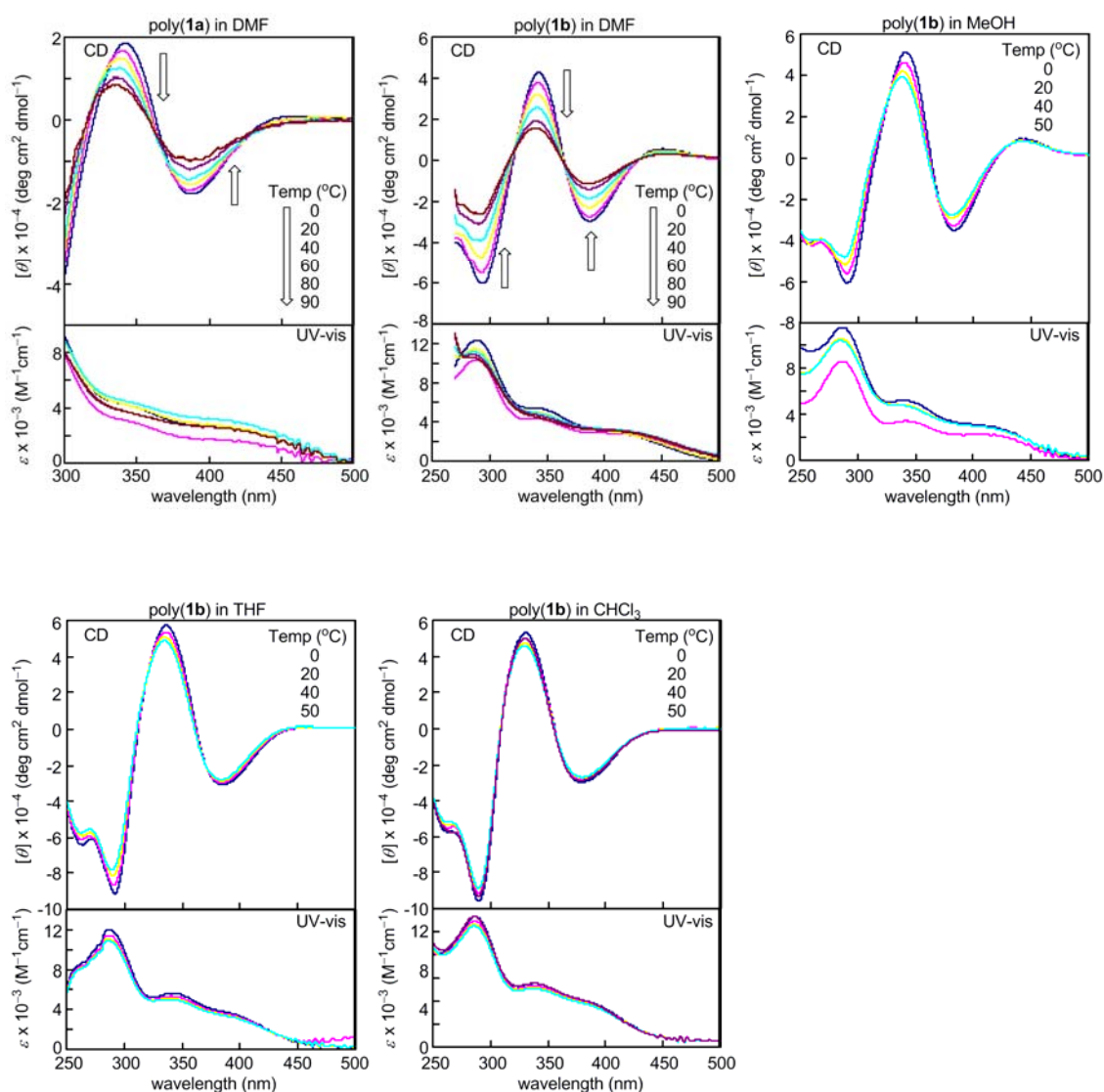


Figure 1. CD and UV-vis spectra of poly(**1a**) measured in DMF and poly(**1b**) measured in DMF, MeOH, THF, and CHCl₃ ($c = 0.20$ mM).

CHCl₃. On the other hand, the Cotton effects gradually decreased the intensities by raising temperature in polar solvents such as MeOH and DMF, indicating that the bias of the screw sense was reduced. Kuhn's dissymmetry factors ($g = \Delta\epsilon/\epsilon$) were calculated to analyze the predominance of screw sense of the helices. Figure 2 displays the g values of poly(**1b**) at 375 nm at various temperatures to determine the temperature effect on the helical sense. Judging from the decrease of g values in DMF, 46% of helix was inverted by raising temperature from 0 to 90 °C in the solvent. The g values at 285 and 330 nm were also decreased upon raising temperature in a fashion to those at 375 nm. In MeOH, the helix seemed to be partly inverted in a manner similar to the case in DMF at a range of 0–50 °C. On the other hand, the g values were slightly decreased in CHCl₃ and THF at the temperature range, indicating the thermal stability of the helical structures in these solvents.

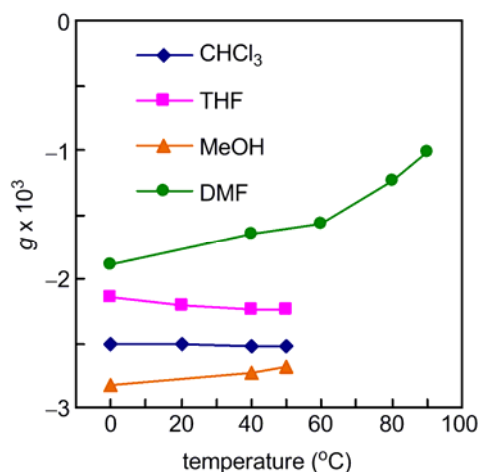


Figure 2. Plots of temperature vs Kuhn's dissymmetry factor (g) of poly(**1b**) calculated from the data at 375 nm in Figure 1.

As described above, polyacetylenes substituted with amide groups stabilize the helical conformation by intramolecular hydrogen bonding between the amide groups.²⁸ The polymers synthesized in this study also have pendent amide groups. Liquid-state

IR spectroscopic study was carried out to determine whether hydrogen bonding contributed to stabilize the helices or not. The IR spectra of **1b** and poly(**1b**) measured in CHCl₃ (2 mM) showed peaks assignable to amide C=O stretching at almost the same wavenumbers (1658 and 1662 cm⁻¹), indicating the absence of intramolecular hydrogen bonding between the amide groups. It is concluded that the helical structure of the polymer is stabilized by steric repulsion between the pendent groups in a manner similar to poly(propiolate)s²⁹ and poly(1-methylpropargyl ester)s.³⁰ This is coincident with the helix formation in polar solvents such as MeOH and DMF, which prevent the amide groups at the polymer side chains from forming hydrogen bonds each other.

The geometries of a helical 18-mer of **1b** were optimized by the molecular mechanics calculation using the MMFF94 force field to elucidate the conformation, where the dihedral angle at the double bond in the main chain was fixed at 0° (*cis*-polyacetylene), and the dihedral angle ϕ at the single bond was varied from 80° to 170° (right-handed helix) and 190° to 280° (left-handed helix) at every 10° increment. As depicted in Figure 3, a right-handed helical conformer with $\phi = 140^\circ$ was the most

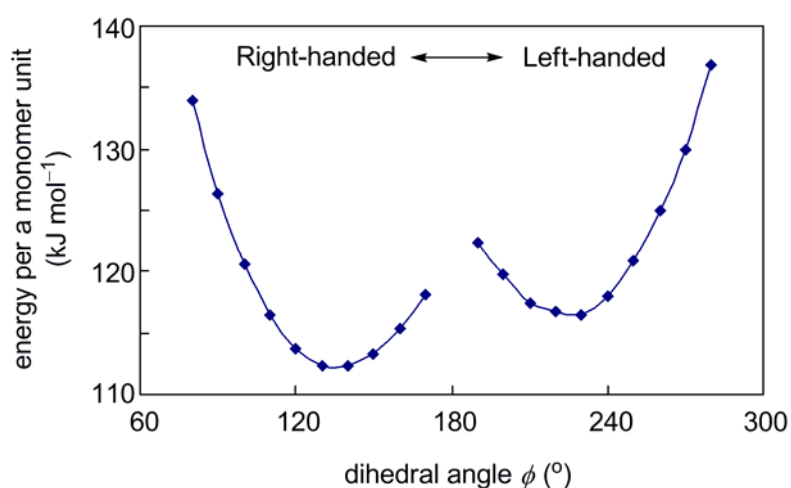


Figure 3. Relationship between the dihedral angle ϕ at the single bond of the main chain of poly(**1b**) (18-mer) and the energy calculated by MMFF94.

stable. As illustrated in Figure 4, the main chain takes a helical conformation and the side chains are helically aligned. There is no hydrogen bond between the amide groups at the side chains.

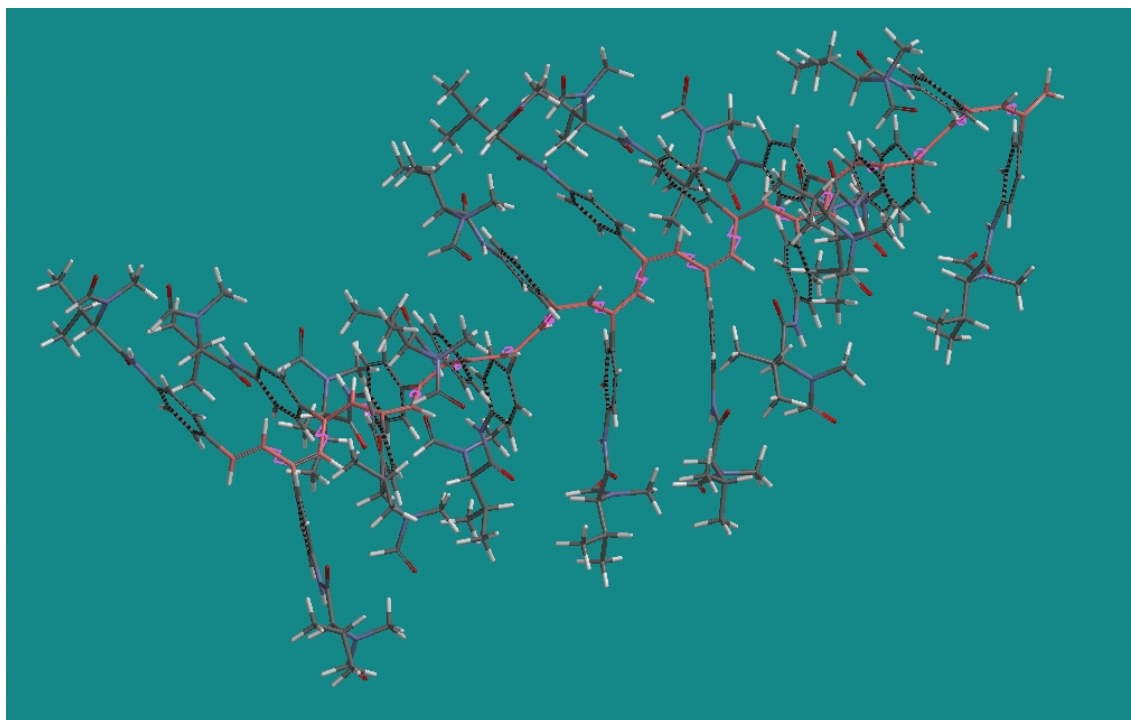


Figure 4. The most stable conformer of poly(**1b**) (18-mer) optimized by MMFF94.

Asymmetric Reduction of Aromatic Ketimine. Table 2 summarizes the results of asymmetric reduction (hydrosilylation followed by hydrolysis) of ketimine **2** in the presence of poly(**1a**) and poly(**1b**) as well as the corresponding monomers **1a** and **1b** as catalysts. Ketimine **2** was satisfactorily reduced to give desired amine **2a** in moderate yields in the presence of the polymers and monomers (runs 2–21). While in the absence of a catalyst (run 1), the product yield was low (34%). As reported in the case of the analogues of **1a** and **1b**, the reduction of **2** catalyzed with *N*-methylvaline derivative **1b** yielded the corresponding amine with an *ee* higher than that with valine derivative **1a**.^{19a} It is considered that *N*-methylation of the amide group leads to high enantioselectivity due to the increase of the conformational bias.

Table 2. Asymmetric Reduction of Ketimine **2**^a

run	catalyst	solvent	time (h)	yield ^b (%)	ee ^c (%)
1	none	CHCl ₃	18	34	— ^d
2	1a	CHCl ₃	18	90	28 (<i>R</i>)
3	1b	CHCl ₃	18	100	78 (<i>R</i>)
4	poly(1a)	CHCl ₃	18	92	16 (<i>S</i>)
5	poly(1b)	CHCl ₃	18	100	18 (<i>S</i>)
6	poly(1b)	THF	18	100	12 (<i>S</i>)
7	poly(1b)	DMF	18	100	0
8	poly(1b)	toluene	18	86	6 (<i>R</i>)
9	poly(1a)	CHCl ₃	3.5	82	16 (<i>S</i>)
10 ^e	poly(1a)	CHCl ₃	3.5	67	20 (<i>S</i>)
11 ^f	poly(1a)	CHCl ₃	3.5	50	16 (<i>S</i>)
12	poly(1b)	CHCl ₃	3.5	83	26 (<i>S</i>)
13 ^e	poly(1b)	CHCl ₃	3.5	77	20 (<i>S</i>)
14 ^f	poly(1b)	CHCl ₃	3.5	58	24 (<i>S</i>)
15 ^g	poly(1b)	CHCl ₃	24	80	10 (<i>S</i>)
16	poly(1a)	THF	3.5	88	2 (<i>R</i>)
17	poly(1b)	THF	3.5	96	14 (<i>S</i>)
18	poly(1a)	DMF	3.5	57	2 (<i>R</i>)
19	poly(1b)	DMF	3.5	39	0
20	poly(1a)	toluene	3.5	43	8 (<i>S</i>)
21	poly(1b)	toluene	3.5	66	6 (<i>R</i>)

^a [**2**]₀ = 0.255 M, [Cl₃SiH] = 0.38 M, [**2**]₀/[catalyst] = 10, r.t., then quenched with quenched with saturated NaHCO₃ aq. ^b Determined by ¹H NMR. ^c Determined by HPLC using a chiral column (Chiralcel OD-H). ^d Not measured. ^e [**2**]₀/[catalyst] = 20. ^f [**2**]₀/[catalyst] = 50. ^g at 0 °C.

On the other hand, the reduction of **2** catalyzed with poly(**1a**) and poly(**1b**) gave **2a** with a predominant configuration opposite to that obtained by the reduction catalyzed with the corresponding monomers (runs 2–5). These results suggest that the chirality of helical conformations of the polymers predominantly determines the configuration of the product rather than that of monomer units. The reduction of **2** proceeded to give **2a** in the presence of poly(**1b**) in THF, DMF, and toluene for 18 hours in high yields (runs 6–8) as well as that in CHCl₃ (run 5), but the *ee* values were lower in the former three solvents. When the reaction time was shortened from 18 to 3.5 hours, both polymers catalyzed the reduction of **2** to give **2a** in CHCl₃ and THF in high yields (runs 9–17) compared in DMF and toluene (runs 18–21). The reduction of **2** afforded **2a** with the highest *ee* in CHCl₃ among the solvents examined. It is considered that DMF also activates trichlorosilane in a manner similar to the polymer catalysts, leading to no enantioselectivity (runs 18 and 19). The low enantioselectivity in toluene is possibly caused by the low solubility of the polymers in the solvent (runs 20 and 21), but the concrete reason is unclear. When the catalyst amount was reduced, the product yield decreased while the enantioselectivity did not so much (runs 9–11 and 12–14). The decrease of reaction temperature did not improve the enantioselectivity (run 15).

Conclusion

In the present study, we have demonstrated the synthesis and polymerization of novel optically active ethynyl monomers derived from valine using a rhodium catalyst to obtain the polymers with moderate molecular weights in good yields. They took helical structures with predominantly one-handed screw sense in solution. They catalyzed the asymmetric reduction of an aromatic ketimine to give an optically active amine, whose predominant chiral configuration was opposite to that obtained by

the reduction catalyzed with the corresponding monomers. To the best of our knowledge, this phenomenon is the first example using asymmetric polymeric catalysts.

Experimental Section

Measurements. ^1H and ^{13}C NMR spectra were recorded on a JEOL EX-400 spectrometer. IR spectra were measured on a JASCO FT/IR-4100 spectrophotometer. Melting points (mp) were measured on a Yanaco micro melting point apparatus. Mass spectra were measured on a JEOL JMS-HX110A mass spectrometer. Specific rotations ($[\alpha]_{\text{D}}$) were measured on a JASCO DIP-100 digital polarimeter with a sodium lamp as a light source. Number- and weight-average molecular weights (M_{n} and M_{w}) of polymers were determined by gel permeation chromatography (GPC) on TSK gel α -M and TSK gel GMH_{XL}, using a solution of LiBr (10 mM) in *N,N*-dimethylformamide (DMF) as an eluent at a flow rate of 1.0 mL/min, calibrated by polystyrene standards at 40 °C.

Materials. All reagents for monomer synthesis were used as purchased without purification. Ketimine **2** was prepared from acetophenone and aniline as described in the literature.³¹ DMF used for polymerization was distilled over calcium hydride. $(\text{nbd})\text{Rh}^+[\eta^6\text{-C}_6\text{H}_5\text{B}^-(\text{C}_6\text{H}_5)_3]$ was prepared by the reaction of $[(\text{nbd})\text{RhCl}]_2$ with $\text{NaB}(\text{C}_6\text{H}_5)_4$ as described in the literature.³²

Monomer Synthesis. *N-tert-Butoxycarbonyl-L-valyl-N'-4-iodobenzene (3a).* 4-[4,6-Dimethoxy-1,3,5-triazin-2-yl]-4-methylmorpholinium chloride (TRIAZIMOH, Tokuyama Co., 3.56 g, 10.9 mmol) was added to a solution of *N-tert*-butoxycarbonyl-L-valine (1.52 g, 6.97 mmol) and 4-iodoaniline (2.00 g, 9.14 mmol) in ethyl acetate (25 mL), and the resulting mixture was stirred at room temperature overnight. It was washed with 0.5 M HCl, saturated NaHCO_3 aq. and

saturated NaCl aq. The organic layer was dried over anhydrous MgSO₄ and concentrated on a rotary evaporator. The residual mass was purified by silica gel column chromatography eluted with hexane/ethyl acetate = 4/1 (v/v) to obtain **3a** as a colorless solid in 73% yield. ¹H NMR (400 MHz, CDCl₃): δ 1.02 [d, *J* = 6.6 Hz, 6H, –CH(CH₃)₂], 1.43 [s, 9H, (CH₃)₃C–], 2.05–2.19 [m, 1H, –CH(CH₃)₂], 4.07–4.18 [m, 1H, >CHCH(CH₃)₂], 5.54 [d, *J* = 7.8 Hz, 1H, –COONH–], 7.18 [d, *J* = 7.8 Hz, 2H, Ar], 7.45 [d, *J* = 7.6 Hz, 2H, Ar], 9.01 [s, 1H, –CONHAr–]. ¹³C NMR (100 MHz, CDCl₃): δ 18.49 and 19.27 [–CH(CH₃)₂], 28.32 [(CH₃)₃C–], 30.80 [–CH(CH₃)₂], 61.05 [>CHCH(CH₃)₂], 80.35 [(CH₃)₃C–], 87.32 [Ar], 121.49 [Ar], 137.50 [Ar], 137.58 [Ar], 156.64 [–NHCOO–], 170.95 [–CONHAr–].

***N*-tert-Butoxycarbonyl-*N*-methyl-L-valyl-*N'*-4-iodobenzene (3b).** The title compound was synthesized from *N*-tert-butoxycarbonyl-*N*-methyl-L-valine and 4-iodoaniline in a manner similar to **3a**. Yield 48%. ¹H NMR (400 MHz, CDCl₃): δ 0.92 and 1.01 [d, *J* = 6.6 Hz, 6H, –CH(CH₃)₂], 1.47 [s, 9H, (CH₃)₃C–], 2.30–2.45 [m, 1H, –CH(CH₃)₂], 2.85 [s, 3H, >NCH₃], 4.05–4.20 [m, 1H, >CHCH(CH₃)₂], 7.28 [d, *J* = 8.8 Hz, 2H, Ar], 7.57 [d, *J* = 8.3 Hz, 2H, Ar], 8.59 [s, 1H, –CONHAr–]. ¹³C NMR (100 MHz, CDCl₃): δ 18.62 and 19.74 [–CH(CH₃)₂], 25.95 [>NCH₃], 28.27 [(CH₃)₃C–], 30.63 [–CH(CH₃)₂], 66.16 [>CHCH(CH₃)₂], 80.71 [(CH₃)₃C–], 87.01 [Ar], 121.43 [Ar], 137.69 [Ar], 157.41 [–N CH₃COO–], 168.98 [–CONHAr–].

***N*-Formyl-L-valyl-*N'*-4-iodobenzene (4a).** Trifluoroacetic acid (TFA, 2.0 mL, 27.0 mmol) was added to a solution of **3a** (2.14 g, 5.12 mmol) in CH₂Cl₂ (25 mL) at 0 °C and the resulting mixture was stirred at room temperature overnight. The resulting solution was concentrated in vacuo to obtain L-valyl-*N'*-4-iodobenzene trifluoroacetate. It was dissolved in formic acid (27 mL) and acetic acid anhydride (22 mL) was added to a solution at 0 °C. The mixture was stirred at room temperature overnight. The resulting solution was concentrated in vacuo and the

residual mass was purified by recrystallization from hexane/ethyl acetate/methanol to obtain **4a** as a colorless solid in 86% yield. ¹H NMR (400 MHz, CDCl₃): δ 1.04 [t, *J* = 7.1 Hz, 6H, -CH(CH₃)₂], 2.16–2.30 [m, 1H, -CH(CH₃)₂], 4.38–4.49 [m, 1H, >CHCH(CH₃)₂], 6.20 [s, 1H, HCONH-], 7.30 [d, *J* = 7.8 Hz, 2H, Ar], 7.63 [d, *J* = 8.3 Hz, 2H, Ar], 7.93 [s, 1H, -CONHAr-], 8.29 [s, 1H, HCONH-]. ¹³C NMR (100 MHz, CDCl₃): δ 18.24 and 19.36 [-CH(CH₃)₂], 30.74 [-CH(CH₃)₂], 58.26 [>CHCH(CH₃)₂], 96.02 [>CHI], 121.86 [Ar], 137.06 [Ar], 138.00 [Ar], 161.35 [HCONH-], 169.65 [-CONHAr-].

***N*-Formyl-*N*-methyl-*L*-valyl-*N'*-4-iodobenzene (4b).** The title compound was synthesized from **3b** in a manner similar to **4a**. Yield 42%. ¹H NMR (400 MHz, CDCl₃): δ 0.92 and 1.04 [d, *J* = 6.0 Hz, 6H, -CH(CH₃)₂], 2.37–2.56 [m, 1H, -CH(CH₃)₂], 2.98 [s, 3H, >NCH₃], 4.34 [d, *J* = 10.1 Hz, 1H, >CHCH(CH₃)₂], 7.29 [d, *J* = 6.3 Hz, 2H, Ar], 7.60 [d, *J* = 7.8 Hz, 2H, Ar], 8.14 [s, 1H, HCONH-], 8.24 [s, 1H, -CONHAr-]. ¹³C NMR (100 MHz, CDCl₃): δ 18.60 and 19.52 [-CH(CH₃)₂], 25.40 [>NCH₃], 31.74 [-CH(CH₃)₂], 63.24 [>CHCH(CH₃)₂], 87.59 [Ar], 121.77 [Ar], 137.85 [Ar], 164.03 [HCONCH₃-], 167.36 [-CONHAr-].

***N*-Formyl-*L*-valyl-*N'*-4-ethynylbenzene (1a).** Compound **4a** (1.42 g, 4.10 mmol), PdCl₂(PPh₃)₃ (30.6 mg, 43.5 μmol), PPh₃ (63.8 mg, 243 μmol), and CuI (90.8 mg, 477 μmol) were fed into a two-neck flask and it was flushed with hydrogen. DMF (15 mL) and triethylamine (6 mL) were added to the solution, and then (trimethylsilyl)acetylene (1.5 mL, 10.6 mmol) was added dropwise to the solution. The mixture was stirred at room temperature overnight. The resulting mixture was concentrated in vacuo and the residual mass was dissolved in ethyl acetate. The solution was washed with 0.5 M HCl and saturated NaCl aq. The organic layer was dried over anhydrous MgSO₄ and concentrated on a rotary evaporator. The residual mass was purified by silica gel column chromatography eluted with ethyl acetate to

obtain *N*-formyl-*L*-valyl-*N'*-4-trimethylsilylethynylbenzene. 1 M Tetrabutylammonium fluoride solution in THF (2.0 mL) was added dropwise to a solution of *N*-formyl-*L*-valyl-*N'*-4-trimethylsilylethynylbenzene in THF (15 mL) and the solution was stirred for 3 h. The resulting solution was concentrated in vacuo, and the residual mass was dissolved in ethyl acetate and washed with 0.5 M HCl and saturated NaCl aq. It was purified by recrystallization from ethyl acetate to obtain **1a** as a colorless solid in 79% yield. Mp 201–203 °C. $[\alpha]_D +9^\circ$ ($c = 0.10$ g/dL in DMF at room temperature). ^1H NMR (400 MHz, CDCl_3): δ 1.04 [t, $J = 7.6$ Hz, 6H, $-\text{CH}(\text{CH}_3)_2$], 2.14–2.30 [m, 1H, $-\text{CH}(\text{CH}_3)_2$], 3.02 [s, 1H, $-\text{C}\equiv\text{CH}$], 4.46–4.60 [m, 1H, $>\text{CHCH}(\text{CH}_3)_2$], 6.38 [s, 1H, $\text{HCONH}-$], 7.42 [d, $J = 8.3$ Hz, 2H, Ar], 7.49 [d, $J = 8.3$ Hz, 2H, Ar], 8.28 [s, 1H, $\text{HCONH}-$], 8.37 [s, 1H, $-\text{CONHAr}-$]. ^{13}C NMR (100 MHz, CDCl_3): δ 18.35 and 19.33 [$-\text{CH}(\text{CH}_3)_2$], 31.14 [$-\text{CH}(\text{CH}_3)_2$], 58.18 [$>\text{CHCH}(\text{CH}_3)_2$], 76.89 [$-\text{C}\equiv\text{CH}$], 83.36 [$-\text{C}\equiv\text{CH}$], 118.32 [Ar], 119.79 [Ar], 132.96 [Ar], 137.99 [Ar], 161.42 [$\text{HCONH}-$], 169.28 [$-\text{CONHAr}-$]. IR (cm^{-1} , KBr): 3295 (NH), 3250 (NH), 3103 (NH), 3045 (Ar), 2972 (CH), 2957 (CH), 2883 (CH), 2106 ($\text{C}\equiv\text{C}$), 1903 (Ar), 1641 (NHCO), 1531, 1507, 1388, 1250, 817. HRMS. Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$ (m/z) 244.1212. Found: 244.1213.

***N*-Formyl-*N*-methyl-*L*-valyl-*N'*-4-ethynylbenzene (1b).** The title compound was synthesized from **4b** in a manner similar to **1b**. Yield 76%. Mp 159–161 °C. $[\alpha]_D -90^\circ$ ($c = 0.10$ g/dL in DMF at room temperature). ^1H NMR (400 MHz, CDCl_3): δ 0.92 and 1.05 [d, $J = 8.1$ Hz, 6H, $-\text{CH}(\text{CH}_3)_2$], 2.40–2.58 [m, 1H, $-\text{CH}(\text{CH}_3)_2$], 2.89 [s, 1H, $-\text{C}\equiv\text{CH}$], 3.04 [s, 3H, $>\text{NCH}_3$], 4.52 [d, $J = 11.2$ Hz, 1H, $>\text{CHCH}(\text{CH}_3)_2$], 7.43 [d, $J = 6.6$ Hz, 2H, Ar], 7.55 [d, $J = 8.6$ Hz, 2H, Ar], 8.17 [s, 1H, $\text{HCONH}-$], 8.83 [s, 1H, $-\text{CONHAr}-$]. ^{13}C NMR (100 MHz, CDCl_3): δ 18.61 and 19.47 [$-\text{CH}(\text{CH}_3)_2$], 25.50 [$>\text{NCH}_3$], 31.68 [$-\text{CH}(\text{CH}_3)_2$], 63.05 [$>\text{CHCH}(\text{CH}_3)_2$], 76.74 [$-\text{C}\equiv\text{CH}$], 83.36 [$-\text{C}\equiv\text{CH}$], 117.70 [Ar], 119.52 [Ar], 132.81 [Ar], 138.32 [Ar],

163.95 [HCONCH₃–], 167.40 [–CONHAr–]. IR (cm^{–1}, KBr): 3299 (NH), 3250 (NH), 3169 (NH), 3080 (Ar), 2965 (CH), 2876 (CH), 2106 (C≡C), 1914 (Ar), 1697 (C=O), 1653 (NHCO), 1598, 1524, 1508, 1405, 1361, 1245, 1084, 843. HRMS. Calcd for C₁₅H₁₈N₂O₂ (*m/z*) 258.3156. Found: 258.1369.

Polymerization. The polymerization was carried out in a glass tube equipped with a three-way stopcock under nitrogen. (nbd)Rh⁺[η^6 -C₆H₅B[–](C₆H₅)₃] (1.0 mg, 2.5 μ mol) was added to a solution of a monomer (0.20 mmol) in DMF (1.0 mL), and the resulting mixture was vigorously stirred. It was kept in a water bath at 30 °C for 12 h. The resulting mixture was poured into diethyl ether (50 mL) to precipitate a polymer. It was separated by filtration using a membrane filter (ADVANTEC H100A047A), and dried under reduced pressure.

Spectroscopic Data of the Polymers. **Poly(1a);** ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.58–1.02 [br, 6H, –CH(CH₃)₂], 1.82–2.19 [br, 1H, –CH(CH₃)₂], 4.24–4.51 [br, 1H, >CHCH(CH₃)₂], 5.54–5.88 [br, 1H, HCONH–], 6.26–6.76 [br, 1H, –CH=C<], 7.11–7.53 [br, 4H, Ar], 7.93–8.31 [br, 1H, –CONHAr–], 8.08 [s, 1H, HCONH–]. IR (cm^{–1}, KBr): 3295 (NH), 3108 (NH), 3040 (Ar), 2965 (CH), 2933 (CH), 2877 (CH), 1663 (NHCO), 1601, 1527, 1404, 1388, 1311, 1189, 838. **Poly(1b);** ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.42–1.38 [br, 6H, –CH(CH₃)₂], 2.20–2.54 [br, 1H, –CH(CH₃)₂], 2.75–3.20 [br, 3H, >NCH₃], 5.60–6.23 [br, 1H, >CHCH(CH₃)₂], 6.23–6.64 [br, 1H, –CH=C<], 6.99–7.51 [br, 4H, Ar], 7.80–8.55 [br, 1H, –CONHAr–], 8.01 [s, 1H, HCONH–]. IR (cm^{–1}, KBr): 3268 (NH), 3103 (NH), 3039 (Ar), 2965 (CH), 2933 (CH), 2873 (CH), 1656 (NHCO), 1600, 1528, 1404, 1314, 1185, 838.

Hydrosilylation of Ketimine 2. Trichlorosilane (38 μ L, 0.38 mmol) was added dropwise to a solution of ketimine **2** (50.0 mg, 0.255 mmol) and in anhydrous CHCl₃ (1.0 mL) at 0 °C, and the mixture was allowed to stir at room temperature

under nitrogen for 18 h. The reaction was quenched with saturated NaHCO₃ aq. (5 mL) and the product was extracted with ethyl acetate (50 mL). The extract was washed with saturated NaCl aq. The organic layer was dried over anhydrous MgSO₄ and concentrated on a rotary evaporator. The residual mass was purified by silica gel column chromatography eluted with hexane/ethyl acetate = 19/1 (v/v) to obtain **2a** as a colorless oil.

References

- (1) (a) List, B.; Lerner, R. A.; Barbas III, C F. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (c) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573.
- (2) (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (b) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208.
- (3) (a) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (b) Jorgensen, K. et al. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790.
- (4) (a) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247. (b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. G. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (c) Bøgevig, A.; Sunden, H.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109. (d) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112.
- (5) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798.
- (6) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.
- (7) (a) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2007**, *129*, 288. (b) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67.
- (8) (a) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 450. (b) Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240. (c) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296. (d) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1790. (e) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (f) Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964. (g) Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Angew. Chem. Int. Ed.*

- 2007**, *46*, 4504. (h) Ibrahem, I.; Rios, R.; Vesely, J.; Hammar, P.; Eriksson, L.; Himio, F.; Córdova, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 4507. (i) Enders, D.; Hüttel, M. R. M.; Grondal, C.; Raabe, G. *Science* **2006**, *441*, 861.
- (9) (a) Inoue, S.; Oku, J. *J. Chem. Soc., Chem. Commun.* **1981**, 229. (b) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910. (c) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *Amino Acids* **1996**, *11*, 259.
- (10) (a) Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929. (b) Budt, K. H.; Vatele, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6080. (c) Takagi, R.; Manabe, T.; Shiraki, A.; Yoneshige, A.; Hiraga, Y.; Kojima, S.; Ohkata, K. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2115. (d) Takagi, R.; Shiraki, A.; Manabe, T.; Kojima, S.; Ohkata, K. *Chem. Lett.* **2000**, 366. (e) Flood, R. W.; Geller, T. P.; Petty, S. A.; Roberts, S. M.; Skidmore, J.; Volk, M. *Org. Lett.* **2001**, *3*, 683. (f) Berkessel, A.; Gasch, N.; Glabitz, K.; Koch, C. *Org. Lett.* **2001**, *3*, 3839.
- (11) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis Vol. I-III*. Springer, Heidelberg, **1999**.
- (12) (a) Xial, D.; Zhang, X. *Angew. Chem. Int. Ed.* **2001**, *40*, 3425. (b) Jiang, X. B.; Minnaard, A. J.; Hessen, B.; Feringa, B. L.; Duchateau, A. L. L.; Andrien, J. G. O.; Boogers, J. A. F.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 1503. (c) Cobley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, *345*, 195. (d) Okuda, J. Verch, S.; Stürmer, R.; Spaniol, T. S. *J. Organomet. Chem.* **2000**, *605*, 55. (e) Samec, J. S. M.; Bäckvall, J. E. *Chem. Eur. J.* **2002**, *8*, 2955.
- (13) (a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis, Vol. I-III*, Springer, Heidelberg, **1999**. (b) Riant, O.; Mostefai, N.; Courmarcel, J. *Synthesis* **2004**, 2943. (c) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779. (d) Lipshutz, B. H.; Shimizu, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 2228.
- (14) (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.
- (15) (a) Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395. (b) Cho, B. T.; Chun, Y. S. *J. Chem. Soc., Perkin. Trans. 1* **1990**, 3200. (b) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1992**, *3*, 1583.
- (16) (a) Ingh, S.; Batra, U. K. *Indian J. Chem.* **1989**, *27*, 1. (b) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (c) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424.

- (17) (a) Malkow, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. *Org. Lett.* **2002**, *4*, 1047. (b) Malkow, A. V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 9659. (c) Malkow, A. V.; Dufková, L.; Farrugia, L.; Kočovský, P. *Angew. Chem.* **2003**, *115*, 3802.
- (18) (a) Iwasaki, F.; Omomura, O.; Mishima, K.; Kanematsu, T.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2001**, *42*, 2525. (b) Iwasaki, F.; Onomura, O.; Mishima, K.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **1999**, *40*, 7507.
- (19) (a) Malkov, A. V.; Mariani, A.; MacDougall, K. N.; Kočovský, P. *Org. Lett.* **2004**, *6*, 2253. (b) Malkov, A. V.; Liddon, A.; Ramirez-Lopez, P.; Bendova, L.; Haigh, D.; Kočovský, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 1432.
- (20) (a) Masuda, T.; Sanda, F. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH:Weinheim, 2003; Vol. 3, pp 375. (b) Nomura, R.; Masuda, T. in Kroshwitz, J. I. editor; *Encyclopedia of Polymer Science and Technology*. New York: Wiley; 2003, Vol. IA, p. 1. (c) Katsumata, T.; Shiotsuki, M.; Masuda, T. *Macromol. Chem. Phys.* **2006**, *207*, 1244. (d) Masuda, T. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 165. (e) Mayershofer, M. G.; Nuyken, O. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 5723. (f) Li, K.; Wei, G.; Darkwa, J.; Pollack, S. K. *Macromolecules* **2002**, *35*, 4573. (g) Wang, R.; Bélanger-Gariépy, F.; Zargarian, D. *Organometallics* **1999**, *18*, 5548.
- (21) (a) Ciardelli, F.; Lanzillo, S.; Pieroni, O. *Macromolecules* **1974**, *7*, 174. (b) Tang, B. Z.; Kotera, N. *Macromolecules* **1989**, *22*, 4388. (c) Yamaguchi, M.; Omata, K.; Hiram, M. *Chem. Lett.* **1992**, *21*, 2261. (d) Aoki, T.; Kokai, M.; Shinohara, K.; Oikawa, E. *Chem. Lett.* **1993**, *22*, 2009. (e) Yashima, E.; Huang, S.; Okamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994**, *15*, 1811. (f) Yashima, E.; Huang, S.; Matsushima, T.; Okamoto, Y. *Macromolecules* **1995**, *28*, 4184. (g) Nakako, H.; Nomura, R.; Tabata, M.; Masuda, T. *Macromolecules* **1999**, *32*, 2861. (h) Nomura, R.; Fukushima, Y.; Nakako, H.; Mauda, T. *J. Am. Chem. Soc.* **2000**, *122*, 8830.
- (22) Tabata, M.; Yang, Y.; Yokota, K. *Polym. J.* **1990**, *22*, 1105.
- (23) Reviews: (a) Yashima, E.; Maeda, K.; Nishimura, T. *Chem. Eur. J.* **2004**, *10*, 42. (b) Lam, J. W. Y.; Tang, B. Z. *Acc. Chem. Res.* **2005**, *38*, 745. (c) Aoki, T.; Kaneko, T.; Teraguchi, M. *Polymer*, **2006**, *47*, 4867.
- (24) (a) Gao, G.; Sanda, F.; Masuda, T. *Macromolecules* **2003**, *36*, 3932. (b) Gao, G.; Sanda, F.; Masuda, T. *Macromolecules* **2003**, *36*, 3938. (c) Sanda, F.; Araki, H.; Masuda, T. *Macromolecules* **2004**, *37*, 8510. (d) Sanda, F.; Terada, K.; Masuda, T. *Macromolecules* **2005**, *38*, 8149.
- (25) (a) Cheuk, K. K. L.; Li, B. S.; Tang, B. Z. In *Encyclopedia of Nanoscience and*

- Nanotechnology*; Nalwa, H. S., Ed.; American Scientific Publishers: Stevenson Ranch, CA, 2004; Vol. 8, p 703. (b) Lai, L. M.; Lam, J. W. Y.; Qin, A.; Dong, Y.; Tang, B. Z. *J. Phys. Chem. B* **2006**, *110*, 11128. (c) Li, B.; Kang, S.; Cheuk, K. K. L.; Wan, L.; Ling, L.; Bai, C.; Tang, B. Z. *Langmuir* **2004**, *20*, 7589.
- (26) (a) Nonokawa, R.; Yashima, E. *J. Am. Chem. Soc.* **2003**, *125*, 1278. (b) Onouchi, H.; Hasegawa, T. Kashiwagi, D.; Ishiguro, H.; Maeda, K.; Yashima, E. *Macromolecules* **2005**, *38*, 8625. (c) Maeda, K.; Tsukui, H.; Matsushita, Y.; Yashima, E. *Macromolecules* **2007**, *40*, 7721.
- (27) (a) Sanda, F. Araki, H.; Masuda, T. *Chem. Lett.* **2005**, *34*, 1642-1643. (b) Maeda, K.; Tanaka, K.; Morino, K.; Yashima, E. *Macromolecules* **2007**, *40*, 6783.
- (28) (a) Nomura, R.; Tabei, J.; Masuda, T. *J. Am. Chem. Soc.* **2001**, *123*, 8430–8431. (b) Tabei, J.; Nomura, R.; Masuda, T. *Macromolecules* **2002**, *35*, 2955–2961. (c) Tabei, J.; Nomura, R.; Masuda, T. *Macromolecules* **2002**, *35*, 5405–5409. (d) Tabei, J.; Nomura, R.; Sanda, F.; Masuda, T. *Macromolecules* **2003**, *36*, 8603–8608. (e) Yue, D.; Fujii, T.; Terada, K.; Tabei, J.; Shiotsuki, M.; Sanda, F.; Masuda, T. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 1515–1524. (f) Suzuki, Y.; Tabei, J.; Shiotsuki, M.; Inai, Y.; Sanda, F.; Masuda, T. *Macromolecules* **2008**, *41*, 1086–1093.
- (29) (a) Nakako, H.; Nomura, R.; Tabata, M.; Masuda, T. *Macromolecules* **1999**, *32*, 2861. (b) Nakako, H.; Mayahara, Y.; Nomura, R.; Tabata, M.; Masuda, T. *Macromolecules* **2000**, *33*, 3978. (c) Nomura, R.; Fukishima, Y.; Nakako, H.; Masuda, T. *J. Am. Chem. Soc.* **2000**, *122*, 8830. (d) Nakako, H.; Nomura, R.; Masuda, T. *Macromolecules* **2001**, *34*, 1496.
- (30) Suzuki, Y.; Shiotsuki, M.; Sanda, F.; Masuda, T. *Macromolecules* **2007**, *40*, 1864–1867.
- (31) (a) Samec, J. S. M.; Bäckvall, J. E. *Chem. Eur. J.* **2002**, *8*, 2955. (b) Schnider, P.; Koch, G.; Pretot, R.; Wang, G.; Bohnen, F. *Chem. Eur. J.* **1997**, *3*, 887.
- (32) Schrock, R. R.; Osborn, J. A. *Inorg. Chem.* **1970**, *9*, 2339.

Part II

Synthesis and Properties of Diketopiperazine-derived Polymers by Polycondensation

Chapter 4

Polycondensation of Diketopiperazine-based Dicarboxylic Acids with Diamines and Dibromoxylenes

Abstract

Aspartic and glutamic acid-based diketopiperazines, *cyclo*(L-asparaginyL-L-asparaginyL) (DKPD) and *cyclo*(L-glutaminyL-L-glutaminyL) (DKPE) were synthesized. Polycondensation of DKPD and DKPE with α,α' -dibromoxylenes was carried out using K_2CO_3 as a base in DMF to obtain polymers with weight-average molecular weights (M_w 's) of 1100–3500. Further, polycondensation of DKPE with various diamines was carried out using 4-[4,6-dimethoxy-1,3,5-triazin-2-yl]-4-methylmorpholinium chloride as a condensation agent in DMF to obtain polymers with M_w 's of 1200–4100. The polymers were insoluble in common organic solvents except DMF.

Introduction

Amino acids are not only biologically relevant substances but also useful for highly pure chiral sources in organic synthesis. Although their structures are simple, they have plural functional groups including hydroxy and mercapto groups as well as amino and carboxy groups, which enable them to be transformed into a wide variety of optically active materials. Polypeptides synthesized from amino acids have been examined as models of proteins; their higher-order structure and catalytic activity for various reactions have been investigated. The attempt to synthesize peptide-mimetic polymers has also been made by means of radical, cationic, and anionic polymerizations, coordination polymerization, polycondensation, and polyaddition of amino acid-based monomers.¹ These peptide-mimetic polymers also attract much attention, because they possibly suppress environmental burden due to biocompatibility and biodegradability in a similar fashion to naturally derived biopolymers.

Diketopiperazine (DKP), the smallest cyclic peptide, is a typical by-product in peptide synthesis. The *s-cis* secondary amide group is directed in a horizontal position to the DKP ring. It has been reported that DKP molecules construct aggregates based on tandem hydrogen bonding between the amide groups in a solid state. The structure of aggregates depends on the amino acid residues forming DKPs. For instance, a glycine-based DKP adopts a linear tape orientation, while an alanine-based one forms a layer-type structure.² The solubility of DKP is commonly low due to the lack of flexibility of the ring bearing amide groups. In recent years, it has been reported that *N*-alkylation of one amide group effectively enhances the solubility, resulting in change of association state.³ These DKPs construct supramolecular architecture utilizing noncovalent bonding such as hydrophobic and electrostatic interaction in addition to hydrogen bonding between the amide groups.

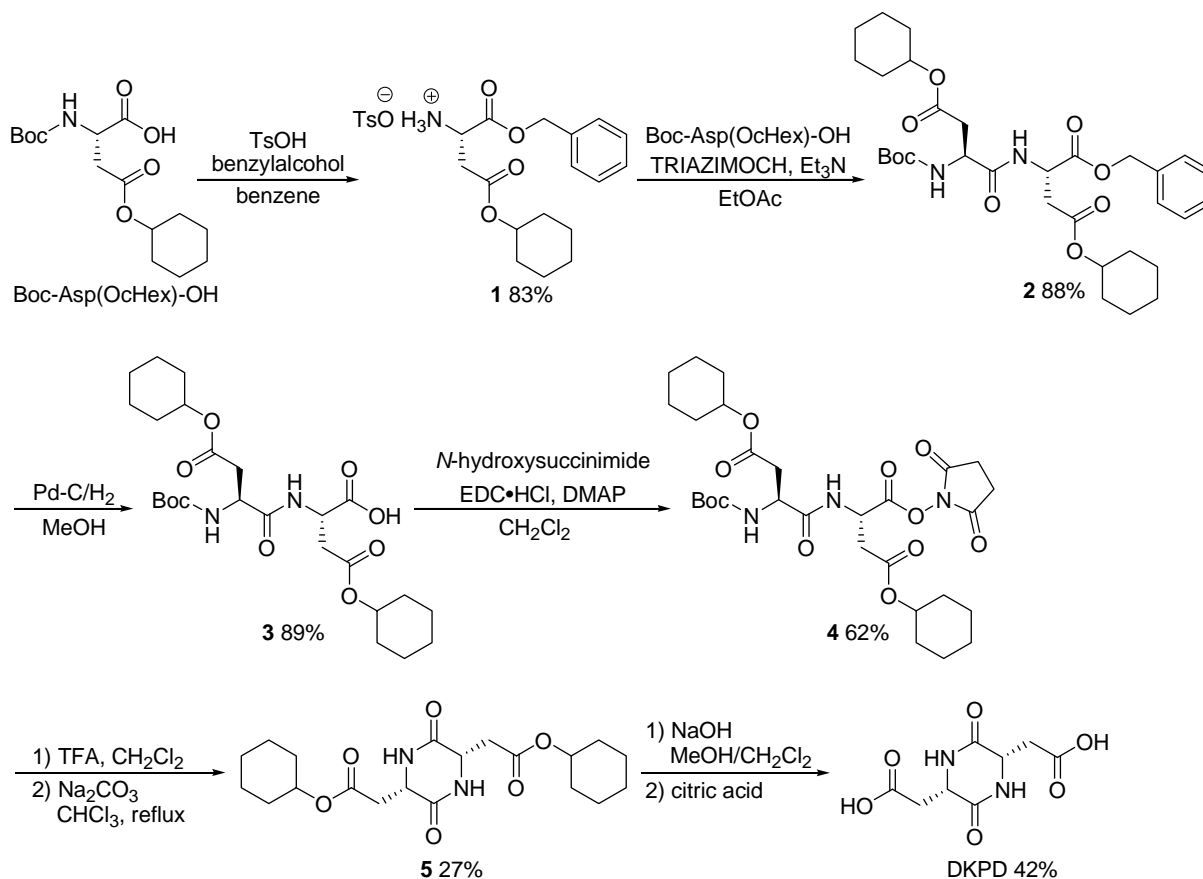
The aggregates show liquid crystallinity⁴ and form microcapsules⁵. Phenylalanine-, aspartic and glutamic acid-based DKPs serve as oil gelators,⁶ wherein intermolecular hydrogen bonding plays a key importance to form molecular network. As described above, DKPs are useful components in the field of supramolecular chemistry. Consequently, synthesis of polymers consisting of DKP units may lead to development of materials showing interesting features based on the chirality and self-assembling properties of DKP. This chapter deals with the synthesis of aspartic and glutamic acid-based dicarboxylated DKPs and their polycondensation with α,α' -dibromoxylenes and diamines.

Results and Discussion

Synthesis of DKPs. DKPE, a glutamic acid-based DKP was prepared by dimerization of pyroglutamic acid (2-carboxy- γ -butyrolactam), followed by hydrolysis.⁷ On the other hand, aspartic acid-based DKPD cannot be synthesized in a similar manner, because pyroaspartic acid (2-carboxy- β -propiolactam) is unstable and unavailable due to large ring strain. The author therefore synthesized DKPD from Boc-Asp(OcHex)-OH according to the route illustrated in Scheme 1. Intramolecular cyclization commonly competes with intermolecular coupling reaction. In the present study, the cyclization through intramolecular ester-amide exchange reaction of a linear dipeptide having *N*-hydroxysuccinimide ester as carboxy terminus successfully proceeded by heating under diluted conditions to give DKP **5**. DKPD was obtained by alkaline hydrolysis of the cyclohexyl ester part of **5**, followed by acidification with citric acid. DKPD was soluble in DMF and DMSO, but insoluble in MeOH, CH₂Cl₂, CHCl₃, benzene, and toluene.

Prior to synthesizing DKP-based polymers, the intermolecular interaction of DKP **5** was examined by ¹H NMR spectroscopy, as commonly done to characterize

Scheme 1



molecular associations,⁸ including the self-association of cyclic secondary *cis*-amide.⁹ The ¹H NMR spectra of **5** were measured in CDCl₃ with various concentrations (1–60 mM) at the temperature ranging from –50 to 50 °C at every 10 °C increment to examine the association of **5**. The chemical shift of the amide NH proton depended both on concentration and temperature as depicted in Figures 1 and 2, where the NH proton signal split due to coupling with chiral methine proton on the DKP ring. Increase in concentration and decrease in temperature resulted in downfield shift of the signal, both of which indicate the formation of intermolecular hydrogen bonding between the amide groups. The ¹H NMR measurement in less polar solvents such as benzene was preferable to that in CDCl₃ to determine the association, but **5** was insoluble in benzene.

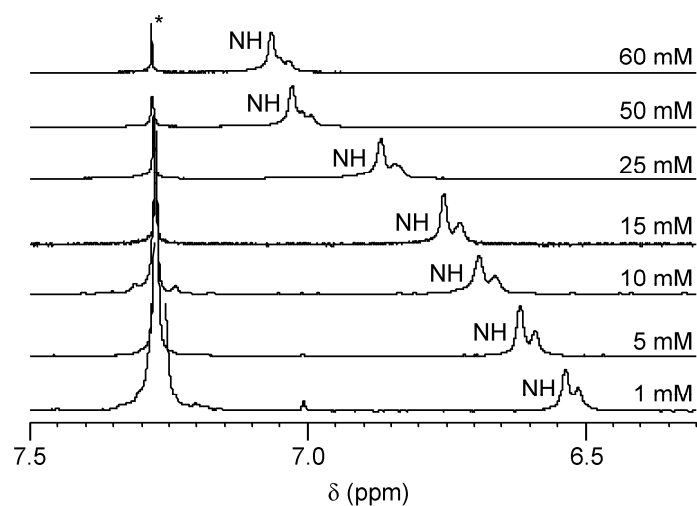


Figure 1. Concentration dependence of the ^1H NMR (400 MHz) chemical shift of the NH proton of **5** measured in CDCl_3 at 0°C . Asterisk represents the signal of CHCl_3 .

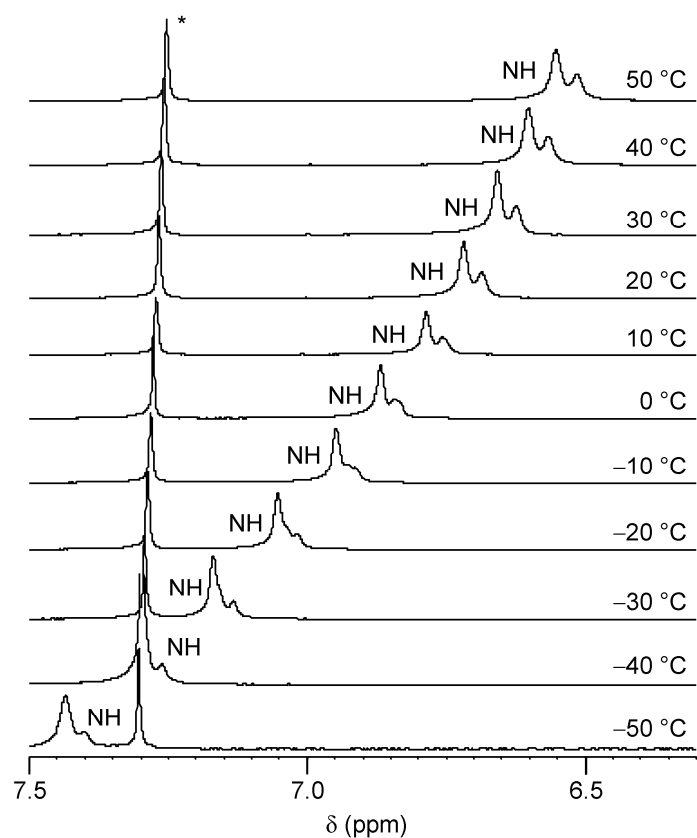


Figure 2. Temperature dependence of the ^1H NMR (400 MHz) chemical shift of the NH proton of **5** measured in CDCl_3 at a concentration of 25 mM. Asterisk represents the signal of CHCl_3 .

Polycondensation of DKPE and DKPD with α,α' -Dibromoxylenes. It is likely that DKP-based polymers carrying benzyl ester moieties are similarly assembled to DKP **5** carrying cyclohexyl ester moieties. The author examined the polycondensations of DKPE and DKPD with α,α' -dibromoxylenes **6–8** to obtain the polymers having DKP benzyl ester structures. The polycondensation was carried out in DMF using potassium carbonate as base at room temperature for 24 h (Scheme 2). Due to the low solubility of DKPD and DKPE in DMF, the monomer concentration was set at 0.2 M, which was relatively low compared to common solution polycondensation.¹⁰ A trace amount of polymeric mass precipitated along with KBr salt in the reaction mixture during polycondensation. The author removed the white precipitate by filtration, and then subjected the filtrate to GPC measurement eluted with DMF without isolating the polymers. At first, the author tried to isolate the polymers by pouring the reaction mixture into 1.0 M HCl, but no polymer precipitated. Along with a GPC peak at a monomer region, a shoulder peak was observed at a molecular weight region around several thousands, which should come from a polymer formed. The M_w 's of the polymers were estimated to be 1100–3500 as summarized in Table 1. The author also concentrated the polymerization mixture on a vacuum pump, and washed the residue with 1.0 M HCl to obtain a small amount of solid. It also showed GPC peaks both at polymer and monomer regions, in which the ratio of the polymer was larger than the case without isolation.

Scheme 2

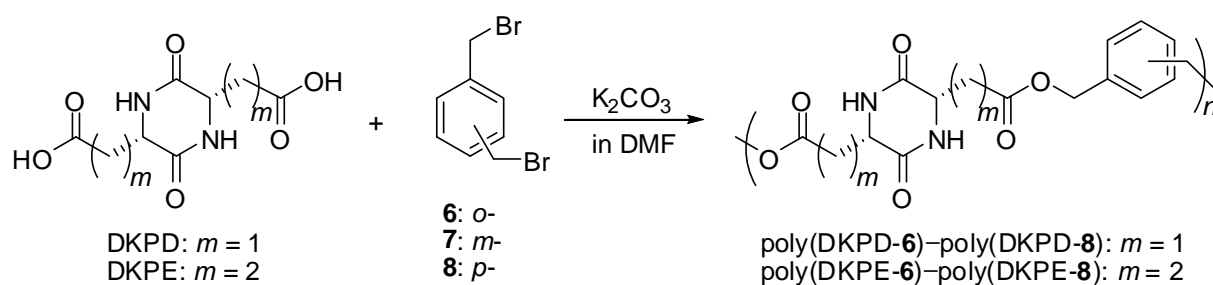


Table 1. Polycondensation of DKPD and DKPE with α,α' -Dibromoxylene^a

run	DKP	α,α' -dibromoxylene	M_w^b	M_w/M_n^b
1	DKPD	6	3400	1.13
2	DKPD	7	1100	1.35
3	DKPD	8	1300	1.28
4	DKPE	6	3500	1.14
5	DKPE	7	3400	1.11
6	DKPE	8	3100	1.12

^a Conditions: [DKP]₀ = [α,α' -dibromoxylene]₀ = 0.20 M, in DMF, room temperature, 24 h. ^b Estimated by GPC based on polystyrene standards, eluent: LiBr solution in DMF (10 mM).

As described above, the molecular weights of the polymers were not high. This is attributable to the relatively low concentration of DKPD and DKPE in DMF in polycondensation due to the low solubility. It seems that the precipitation of a DMF-insoluble polymer also prevented it from increasing the molecular weight. We also examined the polycondensation in DMSO, but the results were unsatisfactory. The polymer yields were not determined in Table 1, because the polymers could not be isolated.

Polycondensation of DKPE with Diamines. The polycondensation of DKPE with diamines **9–14** was carried out using TRIAZIMOXCH as a condensation agent at room temperature for 12 h (Scheme 3). In a manner similar to the polyester synthesis described above, the polycondensation was also performed at a low monomer concentration (0.2 M), because of the low solubility of DKPE in DMF. In runs 3–6 in Table 2, solid gradually precipitated during the polymerization. After a

set time, the DMF-insoluble part was filtered off and the GPC measurement of the

Scheme 3

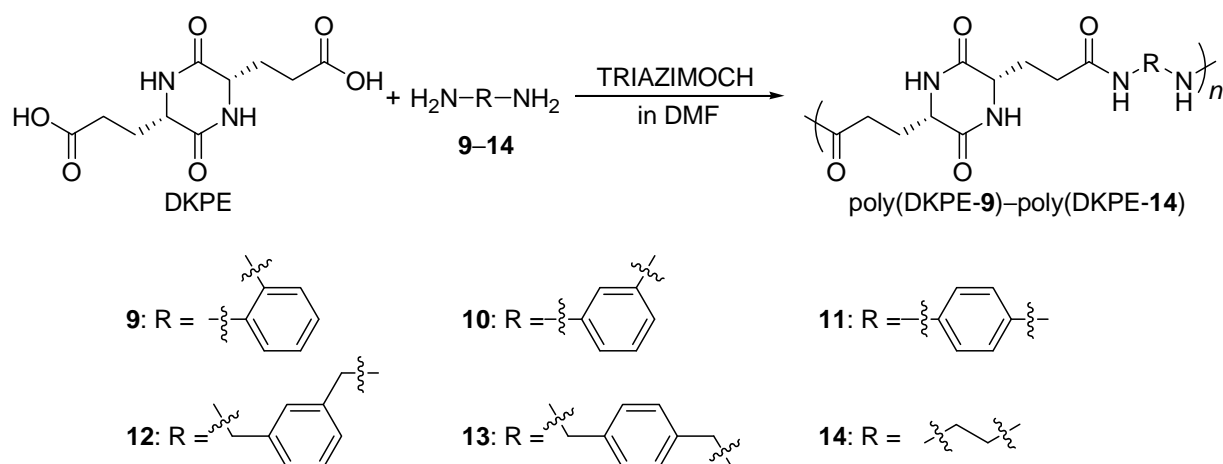


Table 2. Polycondensation of DKPE with Diamines ^a

run	diamine	M_w^b	M_w/M_n^b
1	9	3200	1.07
2	10	2200	1.07
3	11	460	1.24
4	12	4100	3.70
5	13	1200	1.48
6	14	2800	1.06

^a Conditions: [DKPE]₀ = [diamine]₀ = 0.20 M, [4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride] = 0.44 M in DMF, room temperature, 24 h. ^b Estimated by GPC based on polystyrene standards, eluent: LiBr solution in DMF (10 mM).

filtrate was conducted without isolation, because no polymeric mass was obtained when the reaction mixture was poured into 1.0 M HCl. Except run 3, a polymeric GPC peak was observed as a shoulder at a molecular weight region of several

thousands. The M_w 's of the polymers were 1200–4100. It is likely that the low molecular weights are also caused by the low reagent concentration and low solubility of the polymers. The author also examined the polycondensation in DMSO, but the results were unsatisfactory. The polymerization mixtures were insoluble in common organic solvents except DMF and DMSO. The polymer solutions in DMF exhibited negligibly small specific rotations and CD signal, and they showed no birefringence on a polarized optical microscope.

Conclusion

In this chapter, the author has demonstrated the polycondensation of dicarboxylated DKPs with α,α' -dibromoxylenes and diamines to obtain the oligomeric polyesters and polyamides. The polymers exhibited no evidence to take a higher order structure. The author supposes that improvement of solubility of the polymers by introducing long alkyl chains leads to the formation of higher order structure and assembly of DKP-based polymers, because the presence of intermolecular hydrogen bonding of DKP **5** was confirmed by ^1H NMR spectroscopy. Further studies on introducing other functional groups into the polymers are now under progress.

Experimental Section

Measurements. ^1H and ^{13}C NMR spectra were recorded on a JEOL EX-400 spectrometer. IR spectra were measured on a JASCO FT/IR-4100 spectrophotometer. Melting points (mp) were measured on a Yanaco micro melting point apparatus. Mass spectra were measured on a JEOL JMS-HX110A mass spectrometer. Specific rotations ($[\alpha]_D$) were measured on a JASCO DIP-100 digital polarimeter with a sodium lamp as a light source. The number- and weight-average molecular weights (M_n and M_w) of polymers were determined by gel permeation chromatography (GPC)

on TSK gel α -3000, using a solution of LiBr (10 mM) in *N,N*-dimethylformamide (DMF) as an eluent at a flow rate of 1.0 mL/min, calibrated by polystyrene standards at 40 °C.

Materials. All the reagents in monomer synthesis were used as purchased without purification. *cyclo*(L-glutaminyl-L-glutaminyl) (DKPE) was prepared from pyroglutamic acid as described in the literature ($[\alpha]_D = -34^\circ$ (DMSO, $c = 0.10$ g/dL)).⁷ DMF was distilled over calcium hydride.

Monomer Synthesis. *O*-Cyclohexyl-L-aspartic acid benzyl ester tosylate

(1) A solution of *N*-*tert*-butoxycarbonyl-*O*-cyclohexyl-L-aspartic acid (11.0 g, 35.0 mmol) and TsOH•H₂O (7.99 g, 42.0 mmol) in benzyl alcohol (20 mL) and benzene (35 mL) was heated under reflux with a Dean-Stark trap for 3.5 h till water formation stopped. The resulting mixture was added to a solution of ether (60 mL) and hexane (60 mL) to precipitate solid. It was purified by recrystallization with ether/ethanol = 2/1 (v/v) to obtain **1** as a colorless solid in 83% yield.

***N*-*tert*-Butoxycarbonyl-*O*-cyclohexyl-L-asparaginyl-*O*-cyclohexyl-L-aspartic acid benzyl ester (2)** Compound **1** (14.0 g, 29.2 mmol) was dissolved in ethyl acetate (150 mL), and triethylamine (10 mL, 71.9 mmol) was added to the solution at 0 °C. 4-[4,6-Dimethoxy-1,3,5-triazin-2-yl]-4-methylmorpholinium chloride (TRIAZIMOH, Tokuyama Co., 9.79 g, 30.0 mmol) and *N*-*tert*-butoxycarbonyl-*O*-cyclohexyl-L-aspartic acid (9.21 g, 29.2 mmol) were added to the mixture, and the resulting mixture was stirred at room temperature overnight. It was washed with 0.5 M HCl, saturated NaHCO₃ aq., and saturated NaCl aq., and then dried over anhydrous MgSO₄. Ethyl acetate was distilled off using a rotary evaporator. The residual mass was purified by silica gel column chromatography eluted with hexane/ethyl acetate = 4/1 (v/v) to obtain **2** as colorless viscous liquid in 88% yield. ¹H NMR (400 Hz, CDCl₃): δ 1.32–1.81 [m, 29H, –OC(CH₃)₃, –(CH₂)₅–],

2.64–3.02 [m, 4H, –CH₂–], 4.54 [s, 1H, –NHCHCONH–], 4.67–4.81 [m, 2H, OCH<], 4.81–4.93 [m, 1H, –NHCHCOO–], 5.08–5.21 [m, 2H, –OCH₂–], 5.61 [d, *J* = 8.4 Hz, 1H, –NHCO–], 7.28–7.35 [m, 5H, Ar], 7.44 [d, *J* = 8.0 Hz, 1H, –NHCOO–].

***N*-tert-Butoxycarbonyl-*O*-cyclohexyl-L-asparaginyl-*O*-cyclohexyl-L-aspartic acid (3)** Pd-C (10%, 260 mg) was added to a solution of **2** (15.5 g, 25.7 mmol) in methanol (320 mL). The suspension was degassed and flushed with hydrogen gas three times, and then the mixture was stirred at room temperature overnight. Then, the catalyst was filtered off, and the filtrate was concentrated on a rotary evaporator. The residue was dissolved in CHCl₃ and washed with saturated NaCl aq. twice. The organic layer was dried over anhydrous MgSO₄, and concentrated to obtain **3** as a white solid in 89% yield. ¹H NMR (400 Hz, CDCl₃): δ 1.26–1.83 [m, 29H, –OC(CH₃)₃, –(CH₂)₅–], 2.70–3.02 [m, 4H, –CH₂–], 4.59 [s, 1H, –NHCHCONH–], 4.68–4.98 [m, 2H, OCH<], 4.84 [s, 1H, –NHCHCOO–], 5.73 [d, *J* = 4.0 Hz, 1H, –NHCO–], 7.56 [d, *J* = 7.2 Hz, 1H, –NHCOO–], 8.33 [s, 1H, COOH].

***N*-tert-Butoxycarbonyl-*O*-cyclohexyl-L-asparaginyl-*O*-cyclohexyl-L-aspartic acid *N'*-hydroxysuccinimide ester (4)** 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC•HCl, 4.80 g, 25.0 mmol), 4-(dimethylamino)pyridine (DMAP, 302 mg, 2.47 mmol), and *N*-hydroxysuccinimide (2.87 g, 25.0 mmol) was added to a solution of **3** (11.7 g, 22.9 mmol) in CH₂Cl₂ (100 mL) at 0 °C, and then the resulting mixture was stirred at room temperature overnight. Then, CH₂Cl₂ was distilled off using a rotary evaporator, and the residue was dissolved in ethyl acetate. The solution was washed with 0.5 M HCl, saturated NaHCO₃ aq., and saturated NaCl aq., and then dried over anhydrous MgSO₄. Ethyl acetate was evaporated to obtain **4** as a white solid in 62% yield. ¹H NMR (400 Hz, CDCl₃): δ 1.26–1.84 [m, 29H, –OC(CH₃)₃, –(CH₂)₅–], 2.73–3.12 [m, 4H, –CH₂–], 2.83 [s, 4H, –COCH₂CH₂CO–], 4.56 [s, 1H, –NHCHCONH–], 4.76 [m, 2H, OCH<],

added to a suspension of **5** (396 mg, 1.00 mmol) in methanol (10 mL) and CHCl₃ (10 mL) at 0 °C, and stirred at room temperature for 4 h. An excess amount of citric acid was added to the resultant mixture, and it was concentrated on a rotary evaporator. The residual solid was washed with water and CHCl₃ to obtain DKPD as white solid in 42% yield. Mp could not be determined due to decomposition. $[\alpha]_D = -10^\circ$ (DMSO, $c = 0.10$ g/dL). ¹H NMR (400 Hz, DMSO-*d*₆): δ 2.58–2.76 [m, 4H, –CH₂–], 4.08, 4.23 [s, 2H, –NHCHCO–], 8.04 [s, 2H, NH], 12.22 [s, 2H, –COOH]. ¹³C NMR (100 Hz, DMSO-*d*₆): δ 36.95 [>CHCH₂–], 51.21 [–NHCHCO–], 167.22 [–COOH], 171.59 [>CHCONH–]. IR (cm^{–1}, KBr): 3263 (NH), 3082 (NH), 2946, 1713 (C=O), 1643 (NHCO), 1468, 1427, 1327, 1230, 1202. HRMS (m/z) Calcd for C₈H₁₁N₂O₆ 231.0617. Found: 231.0617 [$M+H$]⁺.

Polymerization. Poly(DKPD-6) A solution of DKPD (116 mg, 0.504 mmol), **6** (133 mg, 0.504 mmol), and potassium carbonate (170 mg, 1.24 mmol) in DMF (2.5 mL) was stirred at room temperature for 24 h. The resulting mixture was concentrated and washed with 1.0 M HCl. The residue was isolated by filtration with a membrane filter (pore size 1 μ m), and dried *in vacuo* overnight.

Poly(DKPE-9) A solution of DKPE (130 mg, 0.503 mmol), **9** (54 mg, 0.50 mmol), and TRIAZIMOH (324 mg, 1.21 mmol) in DMF (2.5 mL) was stirred at room temperature for 24 h. The resulting mixture was concentrated and washed with 1.0 M HCl. The residue was isolated by filtration with a membrane filter (pore size 1 μ m), and dried *in vacuo* overnight.

Spectroscopic Data of the Polymers. Poly(DKPD-6); ¹H NMR (400 Hz, DMSO-*d*₆): δ 2.72–2.90 [m, 4H, –CH₂–], 4.11 [s, 2H, –CH–], 5.15 [s, 4H, –CH₂Ar–], 7.24–7.60 [m, 4H, Ar], 8.04–8.22 [m, 2H, NH]. **Poly(DKPD-7);** ¹H NMR (400 Hz, DMSO-*d*₆): δ 2.68–3.00 [m, 4H, –CH₂–], 4.15 [s, 2H, –CH–], 5.09 and 5.16 [s, 4H, –CH₂Ar–], 7.22–7.53 [m, 4H, Ar], 8.21 [s, 2H, NH]. **Poly(DKPD-8);** ¹H NMR (400

Hz, DMSO- d_6): δ 2.68–3.00 [m, 4H, $-\text{CH}_2-$], 4.14 [s, 2H, $-\text{CH}-$], 5.09 and 5.17 [s, 4H, $-\text{CH}_2\text{Ar}-$], 7.30 and 7.34 [s, 4H, Ar], 8.19 [s, 2H, NH]. **Poly(DKPE-6)**; ^1H NMR (400 Hz, DMSO- d_6): δ 1.81–2.13 [m, 4H, $-\text{CHCH}_2-$], 2.27–2.64 [m, 4H, $-\text{CH}_2\text{CO}-$], 3.90 [s, 2H, $-\text{CH}-$], 5.15, 5.24 and 5.28 [s, 4H, $-\text{CH}_2\text{Ar}-$], 7.25–7.61 [m, 4H, Ar], 8.24 [s, 2H, NH]. **Poly(DKPE-7)**; ^1H NMR (400 Hz, DMSO- d_6): δ 1.82–2.11 [m, 4H, $-\text{CHCH}_2-$], 2.36–2.64 [m, 4H, $-\text{CH}_2\text{CO}-$], 3.90 [s, 2H, $-\text{CH}-$], 5.08 and 5.14 [s, 4H, $-\text{CH}_2\text{Ar}-$], 7.22–7.57 [m, 4H, Ar], 8.24 [s, 2H, NH]. **Poly(DKPE-8)**; ^1H NMR (400 Hz, DMSO- d_6): δ 1.85–2.14 [m, 4H, $-\text{CHCH}_2-$], 2.37–2.66 [m, 4H, $-\text{CH}_2\text{CO}-$], 3.90 [s, 2H, $-\text{CH}-$], 5.07 and 5.16 [s, 4H, $-\text{CH}_2\text{Ar}-$], 7.33 [d, $J = 19.6$ Hz, 4H, Ar], 8.23 [s, 2H, NH]. **Poly(DKPE-9)**; ^1H NMR (400 Hz, DMSO- d_6): δ 1.85–2.16 [m, 4H, $-\text{CHCH}_2-$], 2.28–2.46 [m, 4H, $-\text{CH}_2\text{CO}-$], 3.79–4.07 [m, 2H, $-\text{CH}-$], 7.12 and 7.55 [s, 4H, Ar], 8.28 [s, 2H, $-\text{CHNHCO}-$], 9.36 [s, 2H, CONHAr]. **Poly(DKPE-10)**; ^1H NMR (400 Hz, DMSO- d_6): δ 1.76–2.13 [m, 4H, $-\text{CHCH}_2-$], 2.28–2.45 [m, 4H, $-\text{CH}_2\text{CO}-$], 3.66–3.81 [m, 2H, $-\text{CH}-$], 7.08–7.59 [m, 4H, Ar], 8.15–8.41 [m, 2H, $-\text{CHNHCO}-$], 8.88–8.98 [m, 2H, CONHAr]. **Poly(DKPE-11)**; ^1H NMR (400 Hz, DMSO- d_6): δ 1.91–2.12 [m, 4H, $-\text{CHCH}_2-$], 2.26–2.49 [m, 4H, $-\text{CH}_2\text{CO}-$], 3.90 [s, 2H, $-\text{CH}-$], 7.45–7.65 [m, 4H, Ar], 8.23 [s, 2H, $-\text{CHNHCO}-$], 9.88–10.05 [m, 2H, CONHAr]. **Poly(DKPE-12)**; ^1H NMR (400 Hz, DMSO- d_6): δ 1.80–2.09 [m, 4H, $-\text{CHCH}_2-$], 2.17–2.41 [m, 4H, $-\text{CH}_2\text{CO}-$], 3.88 [s, 2H, $-\text{CH}-$], 4.00, 4.23 [s, 4H, CH_2Ar], 7.10–7.54 [m, 4H, Ar], 8.20 [s, 2H, $-\text{CHNHCO}-$], 8.37 [s, 2H, CONHAr]. **Poly(DKPE-13)**; ^1H NMR (400 Hz, DMSO- d_6): δ 1.78–2.06 [m, 4H, $-\text{CHCH}_2-$], 2.08–2.39 [m, 4H, $-\text{CH}_2\text{CO}-$], 3.86 [s, 2H, $-\text{CH}-$], 4.04, 4.22 [s, 4H, CH_2Ar], 7.18 and 7.51 [s, 4H, Ar], 8.181 [s, 2H, $-\text{CHNHCO}-$], 8.34 [s, 2H, CONHAr]. **Poly(DKPE-14)**; ^1H NMR (400 Hz, DMSO- d_6): δ 1.75–2.02 [m, 4H, $-\text{CHCH}_2-$], 2.02–2.25 [m, 4H, $-\text{CH}_2\text{CO}-$], 3.08–3.52 [m, 4H, $-\text{NH}(\text{CH}_2)_2\text{NH}-$] 3.86 [s, 2H, $-\text{CH}-$], 7.90 [s, 2H, CONHAr], 8.17

[s, 2H, –CHNHCO–].

References

- (1) (a) Sanda, F.; Endo, T. *Macromol. Chem. Phys.* **1999**, *200*, 2651. (b) Schlaad, H.; Antonietti, M. *Eur. Phys. J. E.* **2003**, *10*, 17. (c) Löwik, D. W. P. M.; van Hest, J. C. M. *Chem. Soc. Rev.* **2004**, *33*, 234.
- (2) Du, Y.; Creighton, J. C.; Tounge, B. A.; Reitz, A. B. *Org. Lett.* **2004**, *6*, 309.
- (3) Kloster, R. A.; Selby, H. D.; Miller III, W. B.; Mash, E. A. *J. Org. Chem.* **2005**, *70*, 8693.
- (4) Kloster, R. A.; Carducci, M. D.; Mash, E. A. *Org. Lett.* **2003**, *5*, 3683.
- (5) Bergeron, R. J.; Phanstiel IV, O.; Yao, G. W.; Milstein, S.; Weimar, W. R. *J. Am. Chem. Soc.* **1994**, *116*, 8479.
- (6) Hanabusa, K.; Fukui, H.; Suzuki, M.; Shirai, H. *Langmuir* **2005**, *21*, 10383.
- (7) Parrish, D. A.; Mathias, L. J. *J. Org. Chem.* **2002**, *67*, 1826.
- (8) Tsukube, H.; Furuta, H.; Odani, A.; Takeda, Y.; Kudo, Y.; Inoue, Y.; Liu, Y.; Sakamoto, H.; Kimura, K. "Determination of Stability Constants", in: *Comprehensive Supramolecular Chemistry*, 1st edition, Atwood, J.L., Davies, J.E.D., MacNicol, D.D. and Vögtle, F. Eds., Pergamon, New York 1996, p. VIII/425 ff.
- (9) (a) Chen, J. S.; Rosenberger, F. *Tetrahedron Lett.* **1990**, *31*, 3975. (b) Chen, J. S. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 717. (c) Chen, J. S.; Fang, C. Z. *Phys. Chem.* **1997**, *199*, 49.
- (10) Koyama, E.; Sanda, F.; Endo, T. *J. Polym. Sci., Part A; Polym. Chem.* **1997**, *35*, 2925.

Chapter 5

ADMET Polycondensation of Diketopiperazine-based Dienes. Polymerization Behavior and Effect of Diketopiperazine on the Properties of the Formed Polymers

Abstract

L-Glutamic acid diketopiperazine ω -alkenyl esters were synthesized and polymerized via acyclic diene metathesis polycondensation chemistry using ruthenium catalysts. The polycondensation of L-glutamic acid diketopiperazine ω -allyl ester (**1**) was unsuccessful, while the polycondensation of L-glutamic acid diketopiperazine ω -homoallyl ester (**2**), -pentenyl ester (**3**), and -hexenyl ester (**4**) with Grubbs second-generation catalyst and Grubbs-Hoveyda catalyst satisfactorily proceeded to give the corresponding polymers. They exhibited melting temperatures around 150 °C, and possessed crystalline structures similar to that of polyethylene. Dynamic light scattering and differential scanning calorimetric measurements suggested that the polymers formed aggregates in *N,N*-dimethylformamide, presumably based on hydrogen bonding between diketopiperazine moieties.

Introduction

Functional macromolecular materials using biological chiral resources such as amino acids have been gathering much interest due to their biocompatibility and biodegradability easing the environmental burden.¹ Diketopiperazine (DKP), a cyclic amino acid dimer, is a typical by-product in peptide synthesis. It has recently attracted much attention as a bioactive and enzyme-inhibitory compound.² DKP has two *s-cis* secondary amide groups, which can hydrogen bond horizontally along the ring plane. In fact, some DKPs form aggregates based on tandem hydrogen bonding between the amide groups in the solid state. The structure of aggregates depends on the amino acid components of DKPs. For instance, a glycine-based DKP adopts a linear tape orientation, while an alanine-based one forms a layer-type structure.³ The solubility of DKP is commonly low due to the lack of flexibility of the ring bearing amide groups; *N*-alkylation of one amide group effectively enhances the solubility, resulting in a change of association state.⁴ This type of DKP constructs supramolecular architectures utilizing noncovalent bonding such as hydrophobic and electrostatic interactions in addition to hydrogen bonding between the amide groups. Such aggregates show liquid crystallinity⁵ and form microcapsules.⁶ Phenylalanine-, aspartic and glutamic acid-based DKPs serve as oil gelators,⁷ wherein intermolecular hydrogen bonding plays a key role to form molecular networks. Unsymmetrical DKPs consisting of phenylalanine together with histidine or arginine are used as an organocatalyst for asymmetric hydrocyanation.⁸

As described above, DKP derivatives have several interesting features, but only a few approaches to the synthesis of polymers carrying DKPs have been implemented, and the molecular weights and the detail of the properties of the resultant polymers have not been well determined.⁹ The author has recently performed the polycondensation of aspartic and glutamic acid DKPs with various

diamines and dibromoxylenes to obtain polymers with weight-average molecular weights ranging from 1 200 to 4 100.¹⁰ Due to the low solubility and degree of polymerization of the polymers, their properties have not been thoroughly examined.

Among various polycondensation methods, acyclic diene metathesis (ADMET) polycondensation is useful in the synthesis of polymers with precise arrangement of substituents along the polymer's main chain.¹¹ The recent progresses in the development of ruthenium catalysts has enabled polymerization of polar monomers possessing ether, ester, amide, alcohol and carboxylic acid moieties, as well as allowing for the use of polar solvents, owing to their excellent tolerance toward polar functional groups.¹² These catalysts allow amino acid- and peptide-containing monomers to undergo polymerization, leading to development of novel biocompatible polymeric materials.¹³ It is also expected that these polymers form secondary structures like peptides, and are applicable to drug delivery systems, chiral recognition stationary phases, and asymmetric catalysts.¹⁴ The ADMET polycondensation of amino acid- and peptide-based dienes gives polyolefins that form strong films possessing moduli of up to 220 MPa with up to 260% elongation and showing high melting temperatures, which are attractive in biomedical applications.¹⁵ The crystallinity of the polymers largely depends on the amino acid and peptide functionalities. It is expected that incorporation of DKP moieties, which can strongly form hydrogen bonding, will also lead to development of polymers with unique properties. This chapter deals with polycondensation of novel glutamic acid diketopiperazine ω -alkenyl esters using ADMET chemistry.

Results and Discussion

Monomer Synthesis. The author first tried to synthesize DKP monomers **1–4** by condensation of glutamic acid DKP with the corresponding alcohols using a

condensation agent, but failed presumably due to intramolecular condensation forming pyroglutamic acid DKP. Instead, **1–4** were synthesized by acid-catalyzed addition of alcohols to pyroglutamic acid DKP as illustrated in Scheme 1 and were purified by column chromatography and subsequent recrystallization. The structures were determined by ^1H NMR, ^{13}C NMR, and IR spectroscopies as well as high resolution mass spectrometry (HRMS). No impurities were detected in any case.

Scheme 1

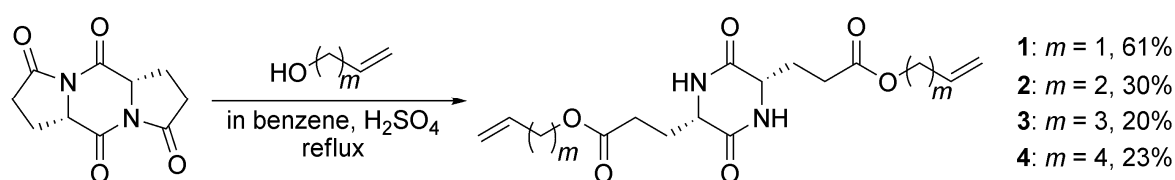
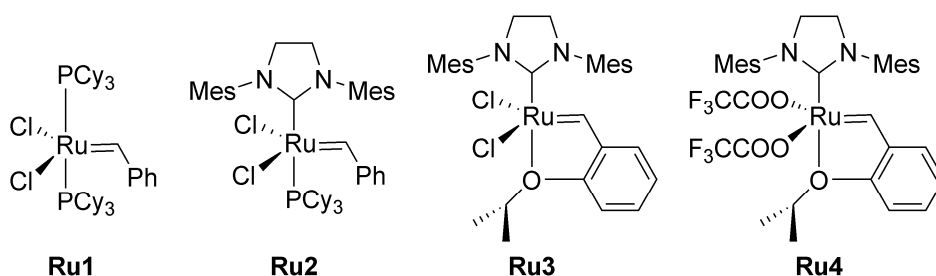


Chart 1. Catalysts for ADMET Polycondensation



ADMET Polycondensation. The ADMET polycondensation of **1–4** was performed with Grubbs and Grubbs-Hoveyda ruthenium complexes **Ru1–Ru4** shown in Chart 1 as catalysts under reduced pressure to remove ethylene gas evolving during the metathesis reaction. At first, the polycondensation of **1–4** was carried out with **Ru1** and **Ru2** at 45 °C. However, neither of these catalysts yielded polymers, and unreacted monomers were recovered. Therefore, the polycondensation temperature was raised to 60 °C in order to promote the metathesis reaction. **Ru3** was also

employed as a catalyst in addition to **Ru1** and **Ru2**, because it has been reported to retain stability and activity even at elevated temperatures.¹⁶ Moreover, the author employed **Ru4**, which catalyzes the metathesis reaction of acetylene derivatives as well as olefins.¹⁷

Table 1 lists the results of the ADMET polycondensation. No polymer was obtained and the monomer was recovered in all the cases of the polycondensation of **1** (runs 1–4). This lack of reactivity is described later. The polycondensation of **2** and **3** with **Ru1** was also unsatisfactory (runs 5 and 10). This catalyst seemed to be unstable and decomposed in DMF at 60 °C, which was indicated by the fact that the brown reaction mixture turned green. In the case of **4**, a polymer with an M_w of 5 300 was obtained with **Ru1**, although the yield was low (run 16).¹⁸ It is considered that **4** is reactive enough to undergo polymerization to some extent before catalyst decomposition by heating. In contrast, the polycondensation mixtures of **2–4** with **Ru2** gradually increased the viscosity to give polymers with M_w 's of 4 500–5 300 (runs 6, 11, and 17).

The polycondensation of **2** with **Ru3** proceeded in a fashion similar to that with **Ru2** to give a polymer with an M_w of 4 000 (run 7). In the polycondensation of **3**, a light brown mass precipitated accompanying the viscosity increase (run 12). In the polycondensation of **4** using **Ru3**, a light brown mass immediately precipitated just after the reaction was initiated (run 18). These masses seem to be high-molecular-weight polymers that do not dissolve in DMF. The polycondensation of **3** and **4** was also carried out in DMSO, but little polymer was isolated in either case (runs 14 and 20). When $[M]_0/[Ru]$ ratio was changed from 50 to 200, the polymer yield largely decreased in the polycondensation of **2** and **3** (runs 8 and 13). At this $[M]_0/[Ru]$ ratio, only the polycondensation mixture of **4** increased the viscosity to give a polymer with an M_w of 4 300 (run 19). **Ru4** was not effective for the ADMET

Table 1. ADMET Polycondensation of 1–4 ^a

run	monomer	cat	polymer			
			yield ^d (%)	M_w ^e	M_w/M_n ^e	$[\alpha]_D$ ^f (deg)
1	1	Ru1	0	—	—	—
2	1	Ru2	0	—	—	—
3	1	Ru3	0	—	—	—
4	1	Ru4	0	—	—	—
5	2	Ru1	0	—	—	—
6	2	Ru2	15	4 600	1.27	—
7	2	Ru3	42	4 000	1.20	—
8 ^b	2	Ru3	2	—	—	—
9	2	Ru4	4	—	—	—
10	3	Ru1	0	—	—	—
11	3	Ru2	31	4 500	1.42	−39
12	3	Ru3	80	12 000	2.12	—
13 ^b	3	Ru3	0	—	—	—
14 ^c	3	Ru3	13	—	—	—
15	3	Ru4	3	—	—	—
16	4	Ru1	5	5 300	1.50	—
17	4	Ru2	46	5 300	1.31	−29
18	4	Ru3	84	15 200	2.66	—
19 ^b	4	Ru3	50	4 300	1.43	—
20 ^c	4	Ru3	14	—	—	—
21	4	Ru4	0	—	—	—

^a Conditions: $[M]_0 = 1.0$ M, $[M]_0/[Ru] = 50$, in DMF, 60 °C, under 100 mmHg, 24 h.

^b $[M]_0/[Ru] = 200$. ^c In DMSO. ^d MeOH-insoluble part. ^e Estimated by GPC based on polystyrene standards, eluent; LiBr solution in DMF (10 mM). ^f Measured by polarimetry at room temperature, $c = 0.10$ g/dL in DMF. $[\alpha]_D$ of monomers, **1**: −22 deg, **2**: −44 deg, **3**: −39 deg, **4**: −29 deg.

polycondensation of the present DKP monomers. **Ru4** is as active as **Ru1**, and less active than **Ru2** in the ring-closing metathesis of diethyl diallylmalonate.^{17a} Therefore, it seems reasonable that **Ru1** and **Ru4** are not effective in the ADMET polycondensation of the present monomers, but the concrete reason of the inactivity is unclear. Polymers obtained could not form self-standing films, presumably due to the relatively low molecular weight and high crystallinity.

Characterization of the Polymers. Poly(**3**) and poly(**4**) obtained by the polymerization with **Ru2** were soluble in DMF and DMSO, but insoluble in CHCl₃. Meanwhile, the **Ru3**-based polymers were hardly soluble in DMF and partly soluble in DMSO. The difference in solubility is attributable to the molecular weight difference. When a small amount of trifluoroacetic acid (TFA) was added to suspensions of poly(**3**) and poly(**4**) in CHCl₃, they became transparent. Judging from a report regarding the formation of a 2:1 cocrystal of TFA and a DKP,⁴ TFA molecules cap the amide moieties disrupting the association of DKPs. This result suggests that the low solubility of the DKP polymers is caused by self-assembling based on hydrogen bonding between the amide groups of the DKP. Meanwhile, the polymers showed $[\alpha]_D$ values similar to those of the monomers in DMF, and no CD signal. These facts indicate that they did not take a chiral secondary structure in the solvent.

Figure 1 shows the DLS histogram of **Ru3**-based poly(**4**) measured in DMF at 80 °C. The peaks around 12 and 113 nm are assignable to unimeric and aggregated polymers, respectively. It was confirmed that the polymer molecules were partially assembled, presumably based on hydrogen bonding between the amide groups of the DKP in DMF.

Figure 2 shows the partial ¹H NMR spectra of **4** and poly(**4**) obtained by the polymerization with **Ru3**. Poly(**4**) exhibited an internal olefin proton signal at 5.4 ppm. The *trans/cis* ratio of the double bonds at the main chain could not be

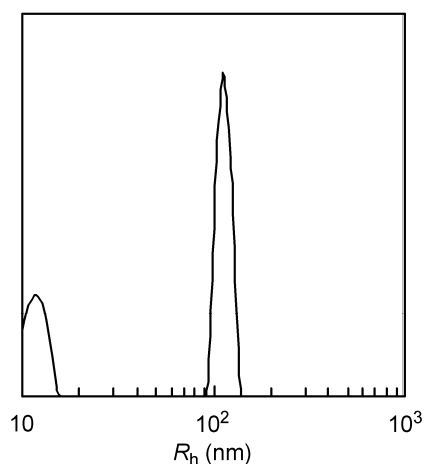


Figure 1. Histogram analysis of DLS of poly(**4**) measured in DMF ($c = 0.5$ wt%) at 80 °C.

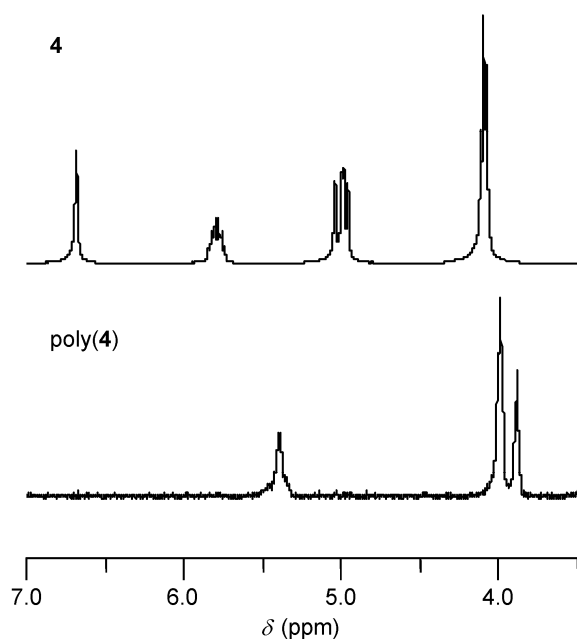


Figure 2. Partial ^1H NMR (400 MHz) spectra of **4** and poly(**4**) measured in $\text{DMSO-}d_6$.

determined by ^1H NMR spectroscopy, because the *trans*- and *cis*-olefin proton signals overlapped each other. It was estimated to be 9/1 by ^{13}C NMR spectroscopy instead (*trans*- and *cis*-olefin carbon signals: 130.0 and 129.3 ppm). Poly(**2**) and poly(**3**) exhibited almost the same *trans/cis* ratio as that of poly(**4**). The internal olefins of polymers obtained via ADMET chemistry are generally *trans*-rich and the results in

this paper are in good agreement with previous work.¹⁹

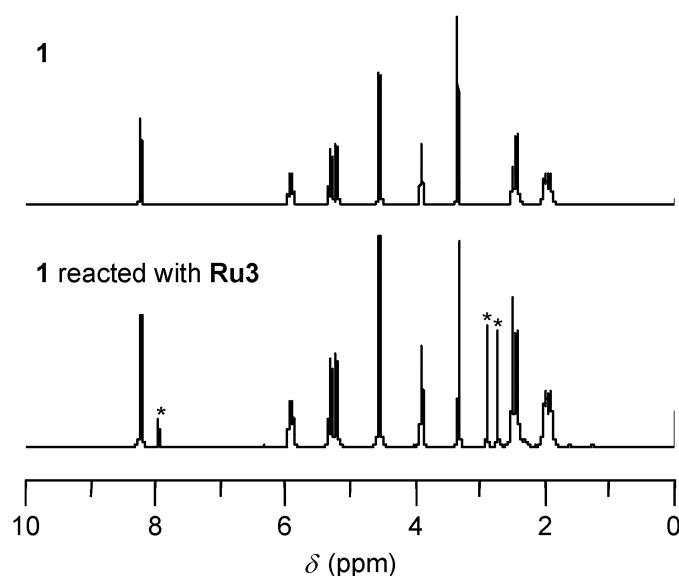
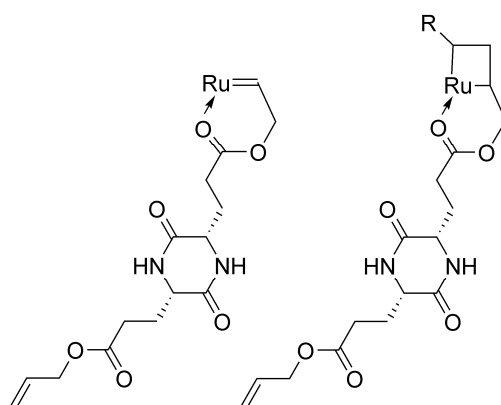


Figure 3. ¹H NMR (400 MHz) spectra of **1** and **1** reacted with **Ru3** measured in DMSO-*d*₆. Asterisks represent the signals of DMF.

There are two possible reasons why no polymer was obtained from allylic ester monomer **1**. One is isomerization of allylic ester into 1-propenyl ester. Ruthenium complexes are well known to catalyze olefin migration in *O*-allyl systems.²⁰ The author measured the ¹H NMR spectra of **1** and a reaction mixture of **1** with **Ru3** to check the possibility. As shown in Figure 3, the two spectra were nearly identical each other, indicating that **1** did not isomerize during the reaction with **Ru3**. No isomerization was confirmed in the polycondensation of **1** with the other ruthenium catalysts, either. Consequently, we consider another reason for no polycondensation of **1**, so called negative neighboring effect.²¹ As illustrated in Chart 2, the oxygen atom possibly coordinates to the ruthenium center to form a six-membered structure, which stabilizes the ruthenium catalyst, resulting in no catalytic activity for ADMET polycondensation. At the same time, the polarization of olefin induced by the ester hinders coordination of olefins and formation of metallocycles. Actually, the

negative charge of olefin terminal carbon atoms of **1** was the smallest among those of the monomers. Considering the fact that allyl esters tend to isomerize into 1-propenyl esters under metathesis conditions,²⁰ this behavior of **1** is somewhat strange. The DKP moiety may also participate in the intramolecular coordination to assist the deactivation of the ruthenium catalysts.

Chart 2. Negative Neighboring Effect



Thermal Properties of the Polymers. The thermal properties of poly(**3**) and poly(**4**) were examined by DSC under nitrogen (Figure 4). They exhibited melting temperatures (T_m) at 153 °C and 159 °C upon heating, and crystallized at 106 °C and 121 °C upon cooling, respectively. Moreover, the author measured the DSC of poly(**4**) in the presence of 0.1–2.0 equiv. of $C_{13}F_{27}COOH$ and 100 equiv. of DMSO. As shown in Figure 4, the addition of $C_{13}F_{27}COOH$ led to disappearance of the exothermic peak at 121 °C derived from crystallization of poly(**4**). On the other hand, the peak still remained upon the addition of as much as 100 equiv. of DMSO. It suggests that the crystallinity of poly(**4**) was based on hydrogen bonding between the amide groups of the DKP moieties of the polymer, and $C_{13}F_{27}COOH$ prohibited the crystallization. We have previously examined the intermolecular interaction of

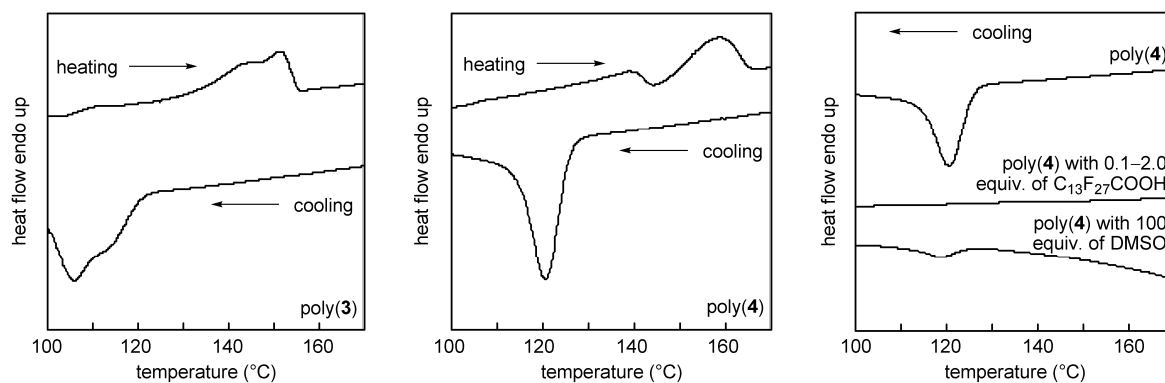
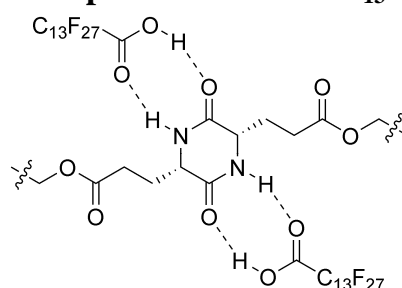


Figure 4. DSC curves of poly(3) and poly(4) (samples: runs 12 and 18 in Table 1) in the absence and presence of 0.1–2.0 equiv. of $C_{13}F_{27}COOH$ and 100 equiv. of DMSO measured in N_2 .

L-aspartic acid DKP cyclohexyl ester by 1H NMR spectroscopy.¹⁰ The chemical shift of the amide NH proton showed a downfield shift with an increase in concentration and decrease in temperature. It indicates the formation of intermolecular hydrogen bonding between the amide groups of DKP moieties. In a similar fashion, the monomeric units in the present study presumably form hydrogen bonding between the amide groups as well, leading to crystallization of the polymers. As described above, DKP forms a complex with TFA based on hydrogen bonding of the amide groups.⁴ In the same way, it is possible for DKP to form hydrogen bonds with $C_{13}F_{27}COOH$ (Chart 3). Consequently, the association of DKP moieties between the polymer chains is disturbed, disrupting the ability of the material to crystallize. Meanwhile,

Chart 3. Complex of DKP and $C_{13}F_{27}COOH$



DMSO did not interrupt this association and the polymers can crystallize in this solvent.

We further investigated the thermal property of poly(**4**) by MDSC (Figure 5). It allows for the separation of the thermal and kinetic components of heat flow signal.²² The data shows that there is a very strong kinetic component to the melting behavior, however almost no contribution from the thermal portion. This is in good agreement with the standard DSC measurements, which show decreases in melting temperature and enthalpy upon subsequent heating scans. This is strong evidence that the crystallization is solely based on aggregates formed in solution, which are not reversible when cooling from the melt.

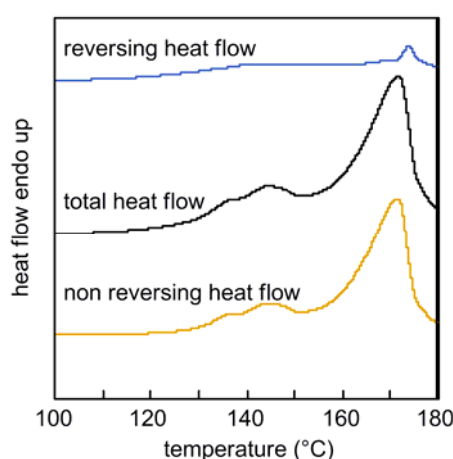


Figure 5. Modulated DSC of poly(**4**) (sample: run 18 in Table 1).

The author also examined the crystalline structure of poly(**4**) by XRD. As shown in Figure 6, XRD peaks were observed at 19.5° and 25.0° , corresponding to the surface distances of 4.55 Å and 3.56 Å, respectively. The former is attributable to the length between the main chains and the latter is attributable to the length between the DKP rings aligned in the horizontal direction. It is considered that the crystalline structure of poly(**4**) is supplemented by hydrogen bonding between the DKP moieties.

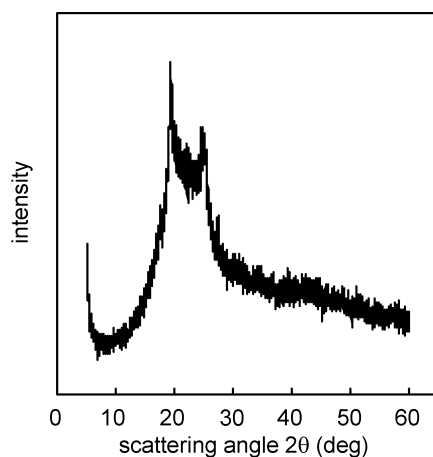


Figure 6. X-ray diffraction pattern for poly(4) (sample: run 18 in Table 1).

Figure 7 depicts the TGA curves of poly(3) and poly(4) obtained with **Ru3**. The onset temperatures of weight loss (T_0) of the polymers were around 200 °C in air, independent of m length and the molecular weights. The polymers decomposed in two steps. It is likely that the ester groups of the polymers were cleaved in the first step. Judging from the unit molecular weights, it is considered that glutamic acid DKPs remained after cleavage of ester groups at the weight residue around 50%.

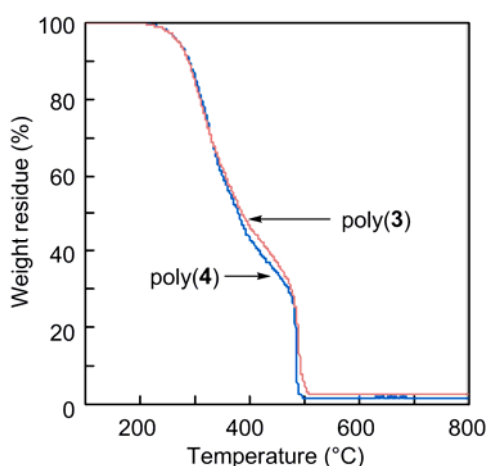


Figure 7. TGA curves of poly(3) and poly(4) (samples: runs 12 and 18 in Table 1) measured in air at a heating rate of 10 °C/min.

Conclusion

In this chapter, the author has demonstrated the ADMET polycondensation of novel glutamic acid diketopiperazine ω -alkenyl esters **1–4** with ruthenium catalysts **Ru1–Ru4**. The polycondensation of **1** was unsuccessful, while the polycondensation of **2–4** with **Ru2** and **Ru3** satisfactorily proceeded to give the corresponding polymers [poly(**2**)–poly(**4**)]. XRD and DSC analyses indicated that the backbones of the polymers crystallized, wherein hydrogen bonding between the DKP moieties possibly assisted the crystallization. In fact, the addition of C₁₃F₂₇COOH caused disappearance of a crystal-based DSC peak of the polymer. DLS measurement of the polymer confirmed that the polymer formed aggregates, presumably based on hydrogen bonding between the DKP moieties. It is expected that the modification of length and structure of the spacer between the DKP and olefin moieties leads to a precise control over thermal and crystalline properties of the polymers.

Experimental Section

Measurements. ¹H and ¹³C NMR spectra were recorded on a JEOL EX-400 spectrometer. IR spectra were measured on a JASCO FT/IR-4100 spectrophotometer. Melting points (mp) were measured on a Yanaco micro melting point apparatus. Mass spectra were measured on a JEOL JMS-HX110A mass spectrometer. Specific rotations ([α]_D) were measured on a JASCO DIP-100 digital polarimeter with a sodium lamp as a light source. The number- and weight-average molecular weights (M_n and M_w) of polymers were determined by gel permeation chromatography (GPC) on TSK gel α -M and TSK gel GMH_{XL}, using a solution of LiBr (10 mM) in *N,N*-dimethylformamide (DMF) as an eluent at a flow rate of 1.0 mL/min, calibrated by polystyrene standards at 40 °C. Dynamic light scattering (DLS) measurements were performed on a Viscotek 802DLS equipped with a 50 mW fiber coupled diode

laser (830 nm), using omniSIZE 3.0 software. Differential scanning calorimetric (DSC) analyses were performed under a nitrogen atmosphere using a Perkin-Elmer PYRIS Diamond DSC. Temperature-modulated differential scanning calorimetric (MDSC) analyses were performed on a TA Instruments Q1000 equipped with a liquid nitrogen cooling accessory calibrated using sapphire and high-purity indium metal. Modulated experiments were scanned at 3 °C/min with a modulation amplitude of 0.4 °C and period of 80 s. XRD measurements were done using a Philips X'Pert MRD system using grazing incidence ($\omega = 3^\circ$). Thermogravimetric analyses (TGA) were conducted in air with a Perkin-Elmer TGA7 thermal analyzer.

Materials. All the reagents for monomer synthesis were used as purchased without purification. *cyclo*(L-Pyroglutaminy-L-pyroglutaminy) was prepared from pyroglutamic acid as described in the literature.²³ DMF and DMSO were distilled over calcium hydride.

Monomer Synthesis. *cyclo*(*O*-Allyl-L-glutaminy-L-glutaminy) (**1**). *cyclo*(L-Pyroglutaminy-L-pyroglutaminy) (3.35 g, 15.1 mmol) and sulfuric acid (6 drops) were added into a solution of allyl alcohol (4.42 g, 76.1 mmol) in benzene (45 mL). The reaction mixture was refluxed for 6 hours until the DKP dissolved, and then concentrated. The residue was dissolved in CHCl₃, and washed with saturated aq. NaHCO₃ and NaCl. The organic layer was dried over anhydrous MgSO₄ and concentrated on a rotary evaporator. It was purified by column chromatography eluted with CHCl₃ and recrystallization from ethanol to obtain **1** as a colorless solid in 61% yield. Mp 142–143 °C, $[\alpha]_D -67^\circ$ ($c = 0.10$ g/dL in CHCl₃ at room temperature). ¹H NMR (400 Hz, DMSO-*d*₆): δ 1.87–2.05 [m, 4H, >CHCH₂–], 2.38–2.47 [m, 4H, –CH₂COO–], 3.91 [t, $J = 5.0$ Hz, 2H, >CHCH₂–], 4.54 [d, $J = 5.2$ Hz, 4H, –COOCH₂–], 5.21 [d, $J = 10.4$ Hz, 2H, –CH=CH₂], 5.30 [d, $J = 17.6$ Hz, 2H, –CH=CH₂], 5.87–5.97 [m, 2H, –CH=CH₂], 8.23 [s, 2H, –CONH–]. ¹³C-NMR (100

Hz, DMSO- d_6): δ 27.94 [$>\text{CHCH}_2-$], 29.16 [$-\text{CH}_2\text{COO}-$], 53.10 [$-\text{NHCHCO}-$], 64.43 [$-\text{COOCH}_2-$], 117.69 [$-\text{CH}=\text{CH}_2$], 132.72 [$-\text{CH}=\text{CH}_2$], 167.77 [$>\text{CHCONH}-$], 171.99 [$-\text{CH}_2\text{COO}-$]. IR (cm^{-1} , KBr): 3321 (NH), 3205 (NH), 3093 ($=\text{CH}$), 2951 (CH), 2877 (CH), 1732 (C=O), 1678 (NHCO), 1446, 1180, 991, 926. HRMS. Calcd for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_6$ (m/z) 338.1478. Found: 338.1476.

***cyclo(O-Butenyl-L-glutaminyl-O-butenyl-L-glutaminyl)* (2).** The title compound was synthesized from *cyclo*(L-pyroglutaminyl-L-pyroglutaminyl) and 3-buten-1-ol in a manner similar to **1**. Yield 30%. Mp 153–154 °C, $[\alpha]_{\text{D}} -62^\circ$ ($c = 0.10$ g/dL in CHCl_3 at room temperature). ^1H NMR (400 Hz, DMSO- d_6): δ 1.85–2.03 [m, 4H, $>\text{CHCH}_2-$], 2.31–2.46 [m, 8H, $-\text{CH}_2\text{COO}-$, $-\text{COOCH}_2\text{CH}_2-$], 3.89 [t, $J = 5.0$ Hz, 2H, $>\text{CHCH}_2-$], 4.07 [t, $J = 6.6$ Hz, 4H, $-\text{COOCH}_2-$], 5.05 [d, $J = 10.4$ Hz, 2H, $-\text{CH}=\text{CH}_2$], 5.11 [d, $J = 17.6$ Hz, 2H, $-\text{CH}=\text{CH}_2$], 5.73–5.84 [m, 2H, $-\text{CH}=\text{CH}_2$], 8.21 [s, 2H, $-\text{CONH}-$]. ^{13}C -NMR (100 Hz, DMSO- d_6): δ 28.01 [$>\text{CHCH}_2-$], 29.26 [$-\text{CH}_2\text{COO}-$], 32.57 [$-\text{CH}_2\text{CH}=\text{CH}_2$], 53.13 [$-\text{NHCHCO}-$], 62.91 [$-\text{COOCH}_2-$], 117.13 [$-\text{CH}=\text{CH}_2$], 134.53 [$-\text{CH}=\text{CH}_2$], 167.74 [$>\text{CHCONH}-$], 172.28 [$-\text{CH}_2\text{COO}-$]. IR (cm^{-1} , KBr): 3321 (NH), 3205 (NH), 3089 ($=\text{CH}$), 2978 (CH), 2873 (CH), 1732 (C=O), 1682 (NHCO), 1446, 1184, 991, 914. HRMS. Calcd for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_6$ (m/z) 366.1791. Found: 366.1797.

***cyclo(O-Pentenyl-L-glutaminyl-O-pentenyl-L-glutaminyl)* (3).** The title compound was synthesized from *cyclo*(L-pyroglutaminyl-L-pyroglutaminyl) and 4-penten-1-ol in a manner similar to **1**. Yield 20%. Mp 143–145 °C, $[\alpha]_{\text{D}} -64^\circ$ ($c = 0.10$ g/dL in CHCl_3 at room temperature). ^1H NMR (400 Hz, DMSO- d_6): δ 1.63–1.70 [m, 4H, $-\text{CH}_2\text{CH}_2\text{CH}_2-$], 1.86–2.10 [m, 8H, $>\text{CHCH}_2-$, $-\text{CH}_2\text{CH}=\text{CH}_2$], 2.33–2.47 [m, 4H, $-\text{CH}_2\text{COO}-$], 3.90 [t, $J = 5.0$ Hz, 2H, $>\text{CHCH}_2-$], 4.01 [t, $J = 6.6$ Hz, 4H, $-\text{COOCH}_2-$], 4.98 [d, $J = 10.4$ Hz, 2H, $-\text{CH}=\text{CH}_2$], 5.04 [d, $J = 17.2$ Hz, 2H, $-\text{CH}=\text{CH}_2$], 5.76–5.86 [m, 2H, $-\text{CH}=\text{CH}_2$], 8.21 [s, 2H, $-\text{CONH}-$]. ^{13}C -NMR (100

Hz, DMSO-*d*₆): δ 27.23 [–CH₂CH₂CH₂–], 28.01 [>CHCH₂–], 29.24 [–CH₂COO–], 29.51 [–CH₂CH=CH₂], 53.14 [–NHCHCO–], 63.30 [–COOCH₂–], 115.25 [–CH=CH₂], 137.74 [–CH=CH₂], 167.74 [>CHCONH–], 172.33 [–CH₂COO–]. IR (cm^{–1}, KBr): 3321 (NH), 3205 (NH), 3085 (=CH), 2970 (CH), 1728 (C=O), 1678 (NHCO), 1446, 1188, 991, 910. HRMS. Calcd for C₂₀H₃₀N₂O₆ (*m/z*) 394.2104. Found: 394.2105.

cyclo(*O*-Hexenyl-L-glutaminyl-*O*-hexenyl-L-glutaminyl) (4). The title compound was synthesized from *cyclo*(L-pyroglutaminyl-L-pyroglutaminyl) and 5-hexen-1-ol in a manner similar to **1**. Yield 23%. Mp 146–147 °C, [α]_D –60° (*c* = 0.10 g/dL in CHCl₃ at room temperature). ¹H NMR (400 Hz, DMSO-*d*₆): δ 1.34–1.42 [m, 4H, –CH₂CH₂CH=CH₂], 1.52–1.59 [m, 4H, –COOCH₂CH₂–], 1.84–2.05 [m, 8H, >CHCH₂–, –CH₂CH=CH₂], 2.31–2.45 [m, 4H, –CH₂COO–], 3.88 [t, *J* = 5.0 Hz, 2H, >CHCH₂–], 4.00 [t, *J* = 6.4 Hz, 4H, –COOCH₂–], 4.93 [d, *J* = 10.0 Hz, 2H, –CH=CH₂], 4.99 [d, *J* = 17.2 Hz, 2H, –CH=CH₂], 5.72–5.82 [m, 2H, –CH=CH₂], 8.19 [s, 2H, –CONH–]. ¹³C-NMR (100 Hz, DMSO-*d*₆): δ 24.63 [–COOCH₂CH₂CH₂–], 27.60 [–COOCH₂CH₂CH₂–], 28.04 [>CHCH₂–], 29.26 [–CH₂COO–], 32.74 [–CH₂CH=CH₂], 53.16 [–NHCHCO–], 63.74 [–COOCH₂–], 114.94 [–CH=CH₂], 138.40 [–CH=CH₂], 167.76 [>CHCONH–], 172.35 [–CH₂COO–]. IR (cm^{–1}, KBr): 3321 (NH), 3209 (NH), 3086 (=CH), 2931 (CH), 1732 (C=O), 1678 (NHCO), 1446, 1184, 995, 910. HRMS. Calcd for C₂₂H₃₄N₂O₆ (*m/z*) 422.2417. Found: 422.2423.

Polymerization. The polymerization was carried out in a glass tube equipped with a three-way stopcock under nitrogen. A ruthenium catalyst was added to a solution of a monomer (0.25 mmol) in DMF (0.25 mL), and the resulting mixture was kept stirring in a water bath at 60 °C for 24 h under reduced pressure (100 mmHg). The polymerization was quenched by adding ethyl vinyl ether (0.1 mL). The

resulting mixture was concentrated with a vacuum pump and the residual mass was washed with MeOH to isolate a polymer. It was separated by filtration using a membrane filter (ADVANTEC H100A047A), and dried under reduced pressure.

Spectroscopic Data of the Polymers. **Poly(2):** ^1H NMR (400 Hz, DMSO- d_6): δ 1.74–2.07 [m, 4H, $>\text{CHCH}_2-$], 2.18–2.48 [m, 8H, $-\text{CH}_2\text{COO}-$, $-\text{CH}_2\text{CH}=\text{CH}_2$], 3.87 [s, 2H, $>\text{CHCH}_2-$], 3.94–4.16 [m, 4H, $-\text{COOCH}_2-$], 5.02 [d, $J = 10.4$ Hz, $-\text{CH}=\text{CH}_2$ of external olefins], 5.09 [d, $J = 17.2$ Hz, $-\text{CH}=\text{CH}_2$ of external olefins], 5.39–5.54 [m, 2H, $-\text{CH}=\text{CH}_2-$], 5.78–5.84 [m, 2H, $-\text{CH}=\text{CH}_2$ of external olefins], 8.20 [s, 2H, $-\text{CONH}-$]. IR (cm^{-1} , KBr): 3317 (NH), 3201 (NH), 3089 ($=\text{CH}$), 2962 (CH), 2893 (CH), 1732 ($\text{C}=\text{O}$), 1678 (NHCO), 1450, 1180, 976.

Poly(3): ^1H NMR (400 Hz, DMSO- d_6): δ 1.53–1.67 [m, 4H, $-\text{CH}_2\text{CH}_2\text{CH}_2-$], 1.83–2.21 [m, 8H, $>\text{CHCH}_2-$, $-\text{CH}_2\text{CH}=\text{CH}_2$], 2.30–2.46 [m, 4H, $-\text{CH}_2\text{COO}-$], 3.89 [s, 2H, $>\text{CHCH}_2-$], 3.99 [t, $J = 6.2$ Hz, 4H, $-\text{COOCH}_2-$], 4.97 [d, $J = 10.0$ Hz, $-\text{CH}=\text{CH}_2$ of external olefins], 5.02 [d, $J = 16.8$ Hz, $-\text{CH}=\text{CH}_2$ of external olefins], 5.35–5.54 [m, 2H, $-\text{CH}=\text{CH}_2-$], 5.77–5.81 [m, 2H, $-\text{CH}=\text{CH}_2$ of external olefins], 8.20 [s, 2H, $-\text{CONH}-$]. IR (cm^{-1} , KBr): 3205 (NH), 3093 ($=\text{CH}$), 2958 (CH), 2900 (CH), 1732 ($\text{C}=\text{O}$), 1678 (NHCO), 1450, 1176, 968.

Poly(4): ^1H NMR (400 Hz, DMSO- d_6): δ 1.24–1.46 [m, 4H, $-\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$], 1.46–1.75 [m, 4H, $-\text{COOCH}_2\text{CH}_2-$], 1.81–2.22 [m, 8H, $>\text{CHCH}_2-$, $-\text{CH}_2\text{CH}=\text{CH}_2$], 2.30–2.48 [m, 4H, $-\text{CH}_2\text{COO}-$], 3.89 [s, 2H, $>\text{CHCH}_2-$], 4.00 [s, 4H, $-\text{COOCH}_2-$], 4.95 [d, $J = 9.6$ Hz, $-\text{CH}=\text{CH}_2$ of external olefins], 5.01 [d, $J = 16.8$ Hz, $-\text{CH}=\text{CH}_2$ of external olefins], 5.39 [m, 2H, $-\text{CH}=\text{CH}-$], 5.72–5.90 [m, 2H, $-\text{CH}=\text{CH}_2$ of external olefins], 8.20 [s, 2H, $-\text{CONH}-$]. IR (cm^{-1} , KBr): 3316 (NH), 3201 (NH), 3093 ($=\text{CH}$), 2938 (CH), 2862 (CH), 1732 ($\text{C}=\text{O}$), 1678 (NHCO), 1450, 1176, 968.

References and Notes

- (1) (a) Sanda, F.; Endo, T. *Macromol. Chem. Phys.* **1999**, *200*, 2651. (b) Schlaad, H.; Antonietti, M. *Eur. Phys. J. E.* **2003**, *10*, 17. (c) Löwik, D. W. P. M.; van Hest, J. C. M. *Chem. Soc. Rev.* **2004**, *33*, 234.
- (2) (a) Martins, M. B.; Carvalho, I. *Tetrahedron* **2007**, *63*, 9923. (b) Peterkofsky, A.; Battaini, F.; Koch, Y.; Takahara, Y.; Dannies, P. *Mol. Cell. Biochem.* **1982**, *42*, 45.
- (3) Du, Y.; Creighton, J. C.; Tounge, B. A.; Reitz, A. B. *Org. Lett.* **2004**, *6*, 309.
- (4) Kloster, R. A.; Selby, H. D.; Miller III, W. B.; Mash, E. A. *J. Org. Chem.* **2005**, *70*, 8693.
- (5) Kloster, R. A.; Carducci, M. D.; Mash, E. A. *Org. Lett.* **2003**, *5*, 3683.
- (6) Bergeron, R. J.; Phanstiel IV, O.; Yao, G. W.; Milstein, S.; Weimar, W. R. *J. Am. Chem. Soc.* **1994**, *116*, 8479.
- (7) Hanabusa, K.; Fukui, H.; Suzuki, M.; Shirai, H. *Langmuir* **2005**, *21*, 10383.
- (8) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910.
- (9) (a) Crescenzi, V.; Giancotti, V.; Quadrifoglio, F. *Makromol. Chem.* **1968**, *120*, 220. (b) Majó, M. A.; Bou, J. J.; Herranz, C.; Muñoz-Guerra, S. *Macromol. Chem. Phys.* **2006**, *207*, 615. (c) Kunisaki, T.; Kawai, K.; Hirohata, K.; Minami, K.; Kondo, K. *J. Polym. Sci. Part A: Polym. Chem.* **2001**, *39*, 927. (d) Akerlund, J.; Harmeier, S.; Pumphrey, J.; Timm, D. C.; Brand, J. I. *J. Appl. Polym. Sci.* **2000**, *78*, 2213.
- (10) Terada, K.; Sanda, F.; Masuda, T. *J. Macromol. Sci., Part A: Pure & Appl. Chem.* **2007**, *44*, 789.
- (11) (a) Lehman, S. E., Jr.; Wagener, K. B. "Handbook of Metathesis", Grubbs, R. H. Ed., Wiley-VCH, Weinheim 2003, Vol. 3, chap. 9. (b) Schwendeman, J. E.; Church, A. C.; Wagener, K. B. *Adv. Synth. Catal.* **2002**, *344*, 597. (c) Baughman, T. W.; Wagener, K. B. *Adv. Polym. Sci.* **2005**, *176*, 1. (d) Matloka, P. P.; Wagener, K. B. *J. Mol. Catal.* **2006**, 257, 89.
- (12) (a) Hong, S. H.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 3508. (b) Vygodskii, Y. S.; Shaplov, A. S.; Lozinskaya, E. I.; Filippov, O. A.; Shubina, E. S.; Bandari, R.; Buchmeiser, M. R. *Macromolecules* **2006**, *39*, 7821. (c) Gallivan, J. P.; Jordan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **2005**, *46*, 2577. (d) Haigh, D. M.; Kenwright, A. M.; Khosravi, E. *Macromolecules* **2005**, *38*, 7571. (e) Lynn, D. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 3187. (f) Lynn, D. M.; Mohr, B.; Grubbs, R. H.; Henling, L. M.; Day, M. W. *J. Am. Chem. Soc.* **2000**, *122*, 6601.
- (13) (a) Maynard, H. D.; Okada, S. Y.; Grubbs, R. H. *Macromolecules* **2000**, *33*,

6239. (b) Maynard, H. D.; Grubbs, R. H. *Macromolecules* **1999**, *32*, 6917. (c) Sutthasupa, S.; Terada, K.; Sanda, F.; Masuda, T. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 5337. (d) Sutthasupa, S.; Terada, K.; Sanda, F.; Masuda, T. *Polymer* **2007**, *48*, 3026.
- (14) (a) Murata, H.; Sanda, F.; Endo, T. *J. Polym. Sci. Part A: Polym. Chem.* **1998**, *36*, 1679. (b) Sanda, F.; Endo, T. *Macromol. Chem. Phys.* **1999**, *200*, 2651. (c) Pino, P. *Adv. Polym. Sci.* **1965**, *4*, 393.
- (15) (a) Hopkins, T. E.; Pawlow, J. H.; Koren, D. L.; Deters, K. S.; Solivan, S. M.; Davis, J. A.; Gómez, F. J.; Wagener, K. B. *Macromolecules* **2001**, *34*, 7920. (b) Hopkins, T. E.; Wagener, K. B. *Macromolecules* **2003**, *36*, 2206. (c) Hopkins, T. E.; Wagener, K. B. *Macromolecules* **2004**, *37*, 1180. (d) Petkovska, V. I.; Hopkins, T. E.; Powell, D. H.; Wagener, K. B. *Macromolecules* **2005**, *38*, 5878. (e) Petkovska, V. I.; Hopkins, T. E.; Powell, D. H.; Wagener, K. B. *Anal. Chem.* **2006**, *78*, 3624.
- (16) (a) Courchay, F. C.; Sworen, J. C.; Wagener, K. B. *Macromolecules* **2003**, *36*, 8231. (b) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H.; *J. Am. Chem. Soc.* **1999**, *121*, 791. (c) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
- (17) (a) Halbach, T. S.; Mix, S.; Fischer, D.; Maechling, S.; Krause, J. O.; Sievers, C.; Blechert, S.; Nuyken, O.; Buchmeiser, M. R. *J. Org. Chem.* **2005**, *70*, 4687. (b) Krause, J. O.; Nuyken, O.; Wurst, K.; Buchmeiser, M. R. *Chem. Eur. J.* **2004**, *10*, 777.
- (18) A LiBr solution in DMF was used as an eluent for SEC measurement, because LiBr prevents amide-containing polymers from aggregation by destroying hydrogen bonding, leading to enhancement of correctness of the measurement.
- (19) (a) Wagener, K. B.; Boncella, J. M.; Nel, J. G. *Macromolecules* **1991**, *24*, 2649. (b) Smith, D. W., Jr.; Wagener, K. B. *Macromolecules* **1993**, *26*, 3533. (c) Lehman, S. E., Jr.; Schwendeman, J. E.; O'Donnell, P. M.; Wagener, K. B. *Inorg. Chim. Acta.* **2003**, *345*, 190. (d) Sworen, J. C.; Smith, J. A.; Wagener, K. B.; Baugh, L. S.; Rucker, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 2228. (e) Boz, E.; Nemeth, A. J.; Ghiviriga, I.; Jeon, K.; Alamo, R. G.; Wagener, K. B. *Macromolecules* **2007**, *40*, 6545.
- (20) Kuźnik, N.; Krompiec, S. *Coord. Chem. Rev.* **2007**, *251*, 222.
- (21) (a) Patton, J. T.; Boncella, J. M.; Wagener, K. B. *Macromolecules* **1992**, *25*, 3862. (b) Wagener, K. B.; Patton, J. T. *Macromolecules* **1993**, *26*, 249. (c) Wagener, K. B.; Brzezinska, K.; Anderson, J. D.; Younkin, T. R.; Steppe, K.; DeBoer, W. *Macromolecules* **1997**, *30*, 7363.
- (22) (a) Jones, K. J.; Kinshott, I.; Reading, M.; Lacey, A. A.; Nikolopoulos, C.;

- Pollock, H. M. *Thermochim. Acta.* **1997**, 304-305, 187. (b) Schawe, J. E. K. *Thermochim. Acta.* **1997**, 304-305, 111. (c) Wunderlich, B. *J. Thermal. Anal.* **2006**, 85, 179. (d) Shieh, Y. T.; Liu, G. L. *J. Polym. Sci., Part B: Polym. Phys.* **2007**, 45, 466.
- (23) Parrish, D. A.; Mathias, L. J. *J. Org. Chem.* **2002**, 67, 1820.

Part III

Synthesis and Self-assemble Properties of Diketopiperazine-derivatives

Chapter 6

Diketopiperazine Supramolecule Derived from Hydroxyphenylglycine

Abstract

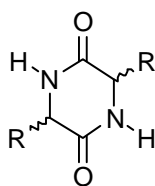
A diketopiperazine (DKP) having long alkyl chains was synthesized from D-*p*-hydroxyphenylglycine, and the formation of supramolecules was examined. The ^1H NMR and UV-vis spectroscopic measurements and molecular modeling have suggested that the DKP molecules are aligned based on hydrogen bonding between the amide groups, and there is no stacking between the phenyl groups.

Introduction

Supramolecules are molecular assemblies formed by noncovalent interaction such as hydrogen bonding, van der Waals interaction, and electrostatic interaction.¹ Among a wide variety of supramolecules, polymeric assemblies formed by repeated intermolecular interactions between monomeric compounds are defined as supramolecular polymers. They attract much attention due to the unique properties such as self-healing and stimuli-responsiveness based on the supramolecular nature, and rheological and mechanical properties based on the polymeric architecture as well.²

Diketopiperazine (DKP, Chart 1), a cyclic amino acid dimer, is a typical by-product in peptide synthesis. It has two *s-cis* secondary amide groups, which can hydrogen bond horizontally along the ring plane. In fact, some DKPs form aggregates based on tandem hydrogen bonding between the amide groups in the solid state.³ Such aggregates show liquid crystallinity⁴ and form microcapsules.⁵ Phenylalanine-, aspartic and glutamic acid-based DKPs serve as oil gelators,⁶ wherein intermolecular hydrogen bonding plays a key role to form molecular networks. We have recently synthesized DKP-containing polyamides and polyesters with moderate molecular weights.⁷ The author has also reported the acyclic diene metathesis polycondensation of glutamic acid DKP ω -alkenyl esters with ruthenium catalysts.⁸ The formed polymers are associated in the solid and solution states based on hydrogen bonding between the DKP moieties.

Chart 1

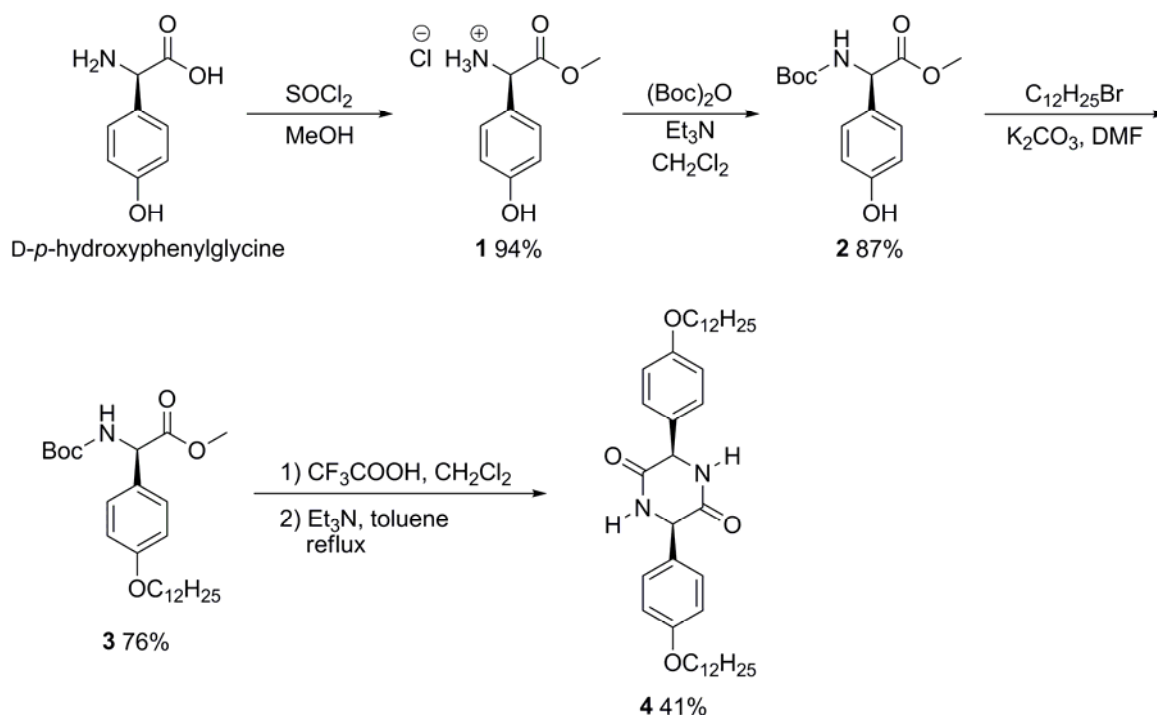


Results and Discussion

In the course of our study on DKP-based polymers, the author has started investigating the synthesis of supramolecular polymers consisting of DKP derivatives. Herein, we wish to report the synthesis of a DKP from *D-p*-hydroxyphenylglycine, and formation of supramolecules.

Common DKPs are poorly soluble in organic solvents due to the aggregation by intermolecular hydrogen bonding between the amide groups. This is important for DKPs to form supramolecular structures as described above, but solubility to a certain extent is preferable for examining the association property spectroscopically. The author therefore designed a symmetrical DKP **4** having long alkyl chains substituted at the benzene ring via the ether linkage to enhance the solubility. Scheme 1 illustrates the synthetic route for **4** starting from *D-p*-hydroxyphenylglycine. DKP **4** was successfully synthesized by direct cyclization of precursor **3** through intramolecular ester-amide exchange reaction by heating at 80 °C for 5 days. The structure was

Scheme 1



confirmed by ^1H NMR, ^{13}C NMR, and IR spectroscopies besides high-resolution mass spectrometry. It was soluble in chloroform and 1,1,2,2-tetrachloroethane at high temperature. The long alkyl chains seem to be effective for enhancing the solubility of **4** as expected.

The intermolecular interaction of **4** was examined by ^1H NMR spectroscopy. Figure 1 depicts the ^1H NMR spectra measured at various concentrations (1–40 mM) in 1,1,2,2-tetrachloroethane- d_2 at 65–100 °C. Since **4** was poorly soluble in chloroform at room temperature, 1,1,2,2-tetrachloroethane- d_2 was used as the measurement solvent. The boiling point of 1,1,2,2-tetrachloroethane- d_2 (147 °C) higher than that of chloroform- d (61 °C) was also suitable for temperature-variable NMR measurement. The chemical shift of the amide NH proton signal depended on both the concentration and temperature as shown in Figure 1. Increase in concentration and decrease in temperature resulted in downfield shift of the signal, both of which indicate the formation of intermolecular hydrogen bonding between the amide groups.

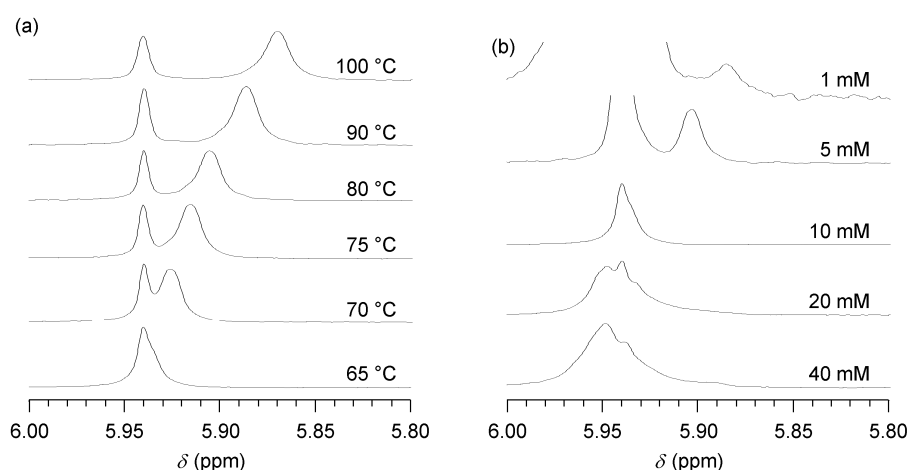


Figure 1. Partial ^1H NMR spectra of **4** measured in 1,1,2,2-tetrachloroethane- d_2 (a) at a concentration of 10 mM at various temperature and (b) at various concentrations at 65 °C.

The UV-vis spectra of **4** were also measured at various concentrations and temperatures. No significant shift of absorption maximum wavelength was observed (Figure 2). This result suggests the absence of intermolecular π -stacking between the benzene rings. This is in good agreement with no change of the chemical shift of the phenyl proton in the ^1H NMR spectra measured at various concentrations and temperatures.

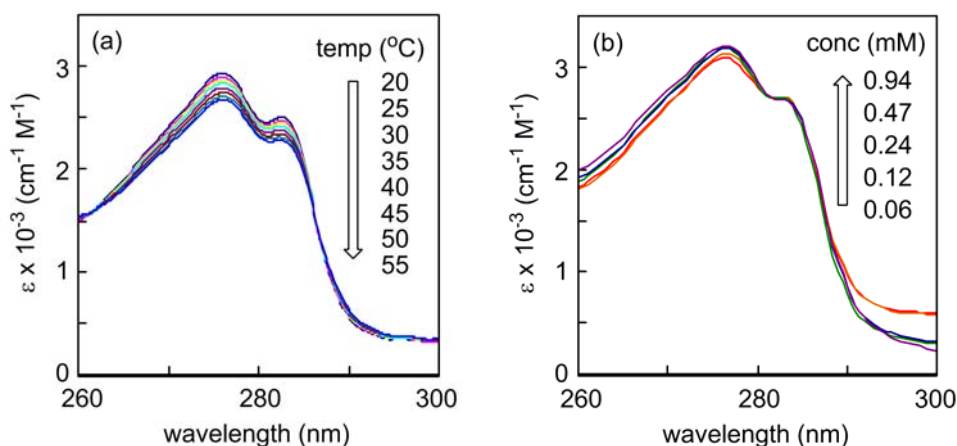


Figure 2. UV-vis spectra of **4** measured in CHCl_3 (a) at a concentration of 0.24 mM at various temperatures and (b) at various concentrations at room temperature.

Figure 3 depicts a possible supramolecular structure consisting of **4** based on the results of ^1H NMR and UV-vis spectroscopic measurements. The geometries were optimized by the molecular mechanics method using the MMFF94 forcefield.¹³ The molecules were aligned horizontally to the DKP rings by hydrogen bonding between the amide groups. The average distance between the benzene rings was 5.8 Å, coincident with the absence of π -stacking. It is implied that hydrophobic interaction between the dodecyl groups contributes to stabilize the supramolecular structure.

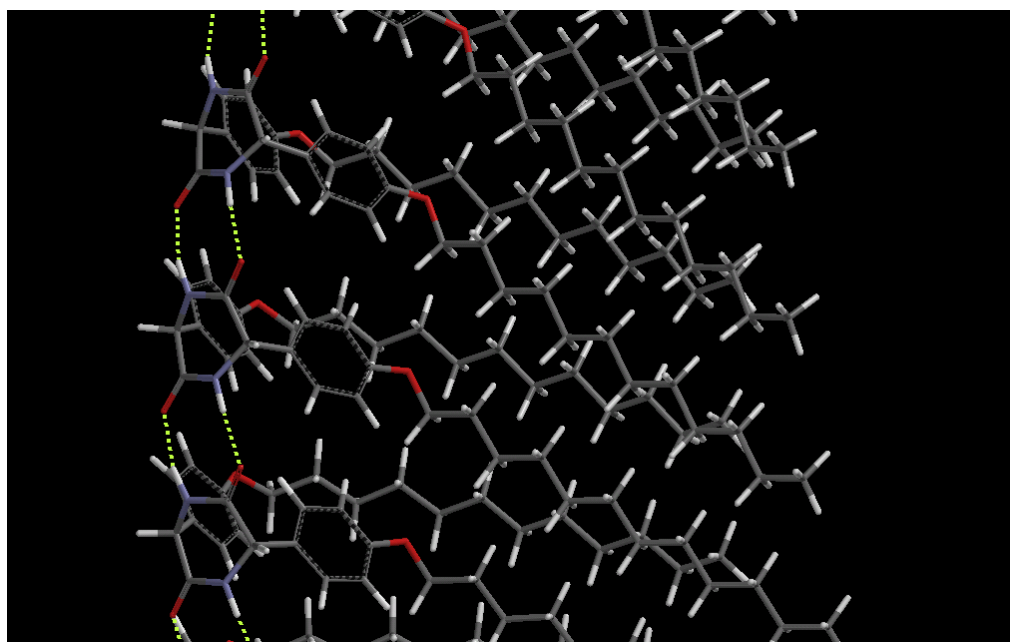


Figure 3. Possible supramolecular structure of **4** optimized by the molecular mechanics calculation using the MMFF94 forcefield. The green dotted lines represent hydrogen bonds between the amide groups.

Conclusion

In this chapter, the author has demonstrated the synthesis of novel DKP **4** having long alkyl chains. DKP **4** was assembled in tetrachloroethane by hydrogen bonding between the amide groups, while the benzene rings did not directly contribute to the aggregation via π -stacking, which was supported by ^1H NMR and UV-vis spectroscopies along with the conformational analysis by the molecular mechanics calculation. It is expected that non-aromatic DKPs substituted with branched alkyl chains show solubility higher than the one in the present study, leading to the development of supramolecules that show chiroptical properties such as liquid crystallinity. Further molecular design of DKP-based supramolecules is under progress.

Experimental Section

Measurements. ^1H and ^{13}C NMR spectra were recorded on a JEOL EX-400 spectrometer. Melting points (mp) were measured on a Yanaco micro melting point apparatus. UV-vis spectra were measured in a quartz cell (thickness: 1 cm) at room temperature using a JASCO J-800 spectropolarimeter.

Materials. All the reagents in monomer synthesis were used as purchased without purification. DMF was distilled over calcium hydride.

Synthesis. **D-*p*-Hydroxyphenylglycine methyl ester hydrochloride (1)** Thionyl chloride (13 mL) was added to MeOH (50 mL) at $-10\text{ }^{\circ}\text{C}$ and the solution was stirred for 10 minutes. D-*p*-Hydroxyphenylglycine (8.36 g, 50.0 mmol) was added to the solution and the resulting mixture was stirred at room temperature overnight. It was concentrated and the residual mass was washed with diethyl ether, and recrystallized with diethyl ether/MeOH to obtain **1** as a colorless solid in 94%. ^1H NMR (400 MHz, DMSO): δ 3.70 [s, 3H, $-\text{CO}_2\text{CH}_3$], 5.10 [s, 1H, $-\text{NCH}<$], 6.83–7.30 [m, 4H, Ar], 8.94 [s, 3H, $-\text{NH}_3$], 9.93 [s, 1H, $-\text{ArOH}$].

N-*tert*-Butoxycarbonyl-D-*p*-hydroxyphenylglycine-O-methyl ester (2) Di-*tert*-butylcarbonate $[(\text{Boc})_2\text{O}]$ (10.3 g, 47.2 mmol) and triethylamine (67.0 mL, 481 mmol) were added to a solution of **1** (10.2 g, 46.9 mmol) in CH_2Cl_2 (400 mL) at $0\text{ }^{\circ}\text{C}$ and the solution was stirred at room temperature overnight. It was concentrated, and then the residue was dissolved in diethyl ether and washed with water twice. The organic layer was dried over anhydrous MgSO_4 and concentrated to obtain **2** as a yellow solid in 87%. ^1H NMR (400 MHz, CDCl_3): δ 1.43 [s, 9H, $-\text{OC}(\text{CH}_3)_3$], 3.71 [s, 3H, $-\text{CO}_2\text{CH}_3$], 5.05 [s, 1H, OH], 5.23 [s, 1H, $-\text{NCH}<$], 5.49 [s, 3H, NH], 6.73–7.18 [m, 4H, Ar].

N-*tert*-Butoxycarbonyl-D-*p*-dodecoxyphenylglycine methyl ester (3) Dodecyl bromide (9.8 mL, 40.9 mmol) was added to a mixture of **2** (11.6 g, 41.2

mmol) and K_2CO_3 (5.67 g, 41.0 mmol) in distilled DMF using a dropping funnel at room temperature under nitrogen. The resulting mixture was heated to 60 °C to be transparent and stirred for 21 hours. The precipitate formed was filtered off and the filtrate was concentrated in vacuo. It was purified by column chromatography eluted with ethyl acetate to obtain **9** as a viscous liquid in 76%. ^1H NMR (400 MHz, CDCl_3): δ 0.88 [t, J = 6.6 Hz, 3H, $-\text{OCH}_2\text{CH}_2(\text{CH}_2)_9\text{CH}_3$], 1.26 [m, 18H, $-\text{OCH}_2\text{CH}_2(\text{CH}_2)_9\text{CH}_3$], 1.43 [s, 9H, $-\text{OC}(\text{CH}_3)_3$], 1.76 [t, J = 7.2 Hz, 2H, $-\text{OCH}_2\text{CH}_2(\text{CH}_2)_9\text{CH}_3$], 3.71 [s, 3H, $-\text{CO}_2\text{CH}_3$], 3.93 [t, J = 6.6 Hz, 2H, $-\text{OCH}_2\text{CH}_2(\text{CH}_2)_9\text{CH}_3$], 5.23 [s, 1H, $-\text{NCH}<$], 5.48 [s, 1H, $>\text{NH}$], 6.85–7.27 [m, 4H, Ar].

cyclo(D-p-Dodecoxyphenylglycinyl-D-p-dodecoxyphenylglycinyl) (4)

Trifluoroacetic acid (TFA, 12 mL, 162 mmol) was added to a solution of **3** (14.1 g, 31.4 mmol) in CH_2Cl_2 (300 mL) using a dropping funnel at 0 °C, and the resulting mixture was stirred at room temperature overnight. CH_2Cl_2 and TFA were distilled off *in vacuo*, and triethylamine (0.2 mL, 1.44 mmol) was added to a solution of the residual mass (446 mg, 1 mmol) in toluene (1 mL) and the reaction mixture was heated to 80 °C for 5 days. After cooling to room temperature, the precipitate formed was separated by filtration to obtain **4** as a colorless solid in 41%. ^1H NMR (400 MHz, 1,1,2,2-tetrachloroethane- d_2): δ 0.87 [t, J = 6.6 Hz, 6H, $-\text{OCH}_2\text{CH}_2(\text{CH}_2)_9\text{CH}_3$], 1.26–1.43 [m, 36H, $-\text{OCH}_2\text{CH}_2(\text{CH}_2)_9\text{CH}_3$], 1.78 [t, J = 7.2 Hz, 4H, $-\text{OCH}_2\text{CH}_2(\text{CH}_2)_9\text{CH}_3$], 3.95 [t, J = 6.6 Hz, 4H, $-\text{OCH}_2\text{CH}_2(\text{CH}_2)_9\text{CH}_3$], 5.06 [s, 2H, $>\text{NCH}<$], 5.94 [s, 2H, $>\text{NH}$], 6.86–7.30 [m, 8H, Ar]. ^{13}C NMR (100 MHz, 1,1,2,2-tetrachloroethane- d_2): δ 14.37 [$-\text{OCH}_2\text{CH}_2(\text{CH}_2)_9\text{CH}_3$], 22.92, 26.28, 29.55, 29.85, and 32.14 [$-\text{OCH}_2\text{CH}_2(\text{CH}_2)_9\text{CH}_3$], 68.69 [$-\text{OCH}_2\text{CH}_2(\text{CH}_2)_9\text{CH}_3$], 74.77 [$>\text{NCH}<$], 115.65 [Ar], 128.53 [Ar], 128.65 [Ar], 160.11 [Ar], 167.01 [$\text{C}=\text{O}$]. IR (cm^{-1} , KBr): 3198 (NH), 3094 (Ar), 2955 (CH), 2918 (CH), 2850 (CH), 1667 (NHCO),

1515, 1457, 1258, 822. Mp (Decomposed at 218–220 °C). HRMS. Calcd for C₂₄H₃₂N₂O₄ (*m/z*) 634.4710. Found: 634.4709.

References and Notes

- (1) (a) Palmans, A. R. A.; Meijer, E. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 8948.
(b) Sijbesma, R. P.; Meijer, E. W. *Chem. Commun.* **2003**, 5. (c) Mateos-Timoneda, M. A.; Crego-Calama, M.; Reinhoudt, D. N. *Chem. Soc. Rev.* **2004**, *33*, 363. (d) Binder, W. H. *Monatshfte für Chemie* **2005**, *136*, 1.
- (2) (a) Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W. Sijbesma, R. P. *Chem. Rev.* **2001**, *101*, 4071. (b) Bouteiller, L. *Adv. Polym. Sci.* **2007**, *207*, 79.
- (3) Du, Y.; Creighton, J. C.; Tounge, B. A.; Reitz, A. B. *Org. Lett.* **2004**, *6*, 309.
- (4) Kloster, R. A.; Carducci, M. D.; Mash, E. A. *Org. Lett.* **2003**, *5*, 3683.
- (5) Bergeron, R. J.; Phanstiel IV, O.; Yao, G. W.; Milstein, S.; Weimar, W. R. *J. Am. Chem. Soc.* **1994**, *116*, 8479.
- (6) Hanabusa, K.; Fukui, H.; Suzuki, M.; Shirai, H. *Langmuir* **2005**, *21*, 10383.
- (7) Terada, K.; Sanda, F.; Masuda, T. *J. Macromol. Sci., Part A: Pure & Appl. Chem.* **2007**, *44*, 789.
- (8) Terada, K.; Berda, E. B.; Wagener, K. B.; Sanda, F.; Masuda, T. *Macromolecules* **2008**, *41*, 6041.
- (9) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490. The molecular mechanics calculation was carried out with Wavefunction Inc., Spartan '06 Windows.

Chapter 7

Synthesis of Novel Diketopiperazine-derivative and Observation of Self-assembled Structure

Abstract

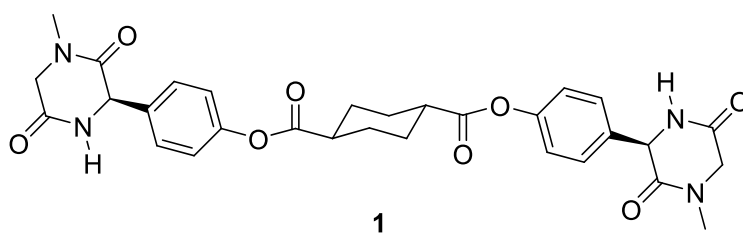
An *N*-monomethylated unsymmetrical diketopiperazine was synthesized from *D*-*p*-hydroxyphenylglycine and sarcosine, and condensed with *trans*-1,4-cyclohexanedicarboxylic acid to obtain the ester having diketopiperazine moieties at the both termini. Atomic force microscope measurement indicated that the ester formed a supramolecular structure aligned in a circular pattern based on hydrogen bonding between the amide groups of the diketopiperazine moieties.

Introduction

Diketopiperazine (DKP), the smallest cyclic peptide, has two *s-cis* amide groups that form tandem hydrogen-bonding strands.¹ This nature enables DKPs to take regulated higher order structures such as liquid crystalline² and microcapsules³ by appropriately modifying the side chains. Phenylalanine-, aspartic and glutamic acid-based DKPs serve as oil and ionic liquid gelators⁴ due to the strong ability to form intermolecular hydrogen bonding even in the presence of large amount of solvents. In the field of polymer chemistry, several attempts have been made to utilize DKPs as components of polymers that largely interact with polymeric and monomeric compounds. The author has recently reported the polycondensation of acidic amino acid DKPs with various diamines and dibromoxylenes to obtain polyamides and polyesters.⁵ The author has also performed the acyclic diene metathesis polycondensation of glutamic acid DKP ω -alkenyl esters with ruthenium catalysts.⁶ The formed polymers are associated in the solid and solution states based on hydrogen bonding between the DKP moieties.

DKP derivatives are commonly poorly soluble in solvents due to the lack of flexibility of the DKP ring, which is caused by the confinement of the amide groups to the ring, as well as self-assembling based on hydrogen bonding between the amide groups. The author has confirmed that DKPs having long alkyl groups aggregate based on hydrophobic interaction between the alkyl groups together with hydrogen bonding.⁷ In this chapter, the author synthesizes a novel *trans*-1,4-cyclohexanedicarboxylate **1** substituted with an unsymmetrical DKP consisting of *D-p*-hydroxyphenylglycine and sarcosine (Chart 1), and observes aggregates at the solid state by atomic force microscope (AFM) measurement.

Chart 1



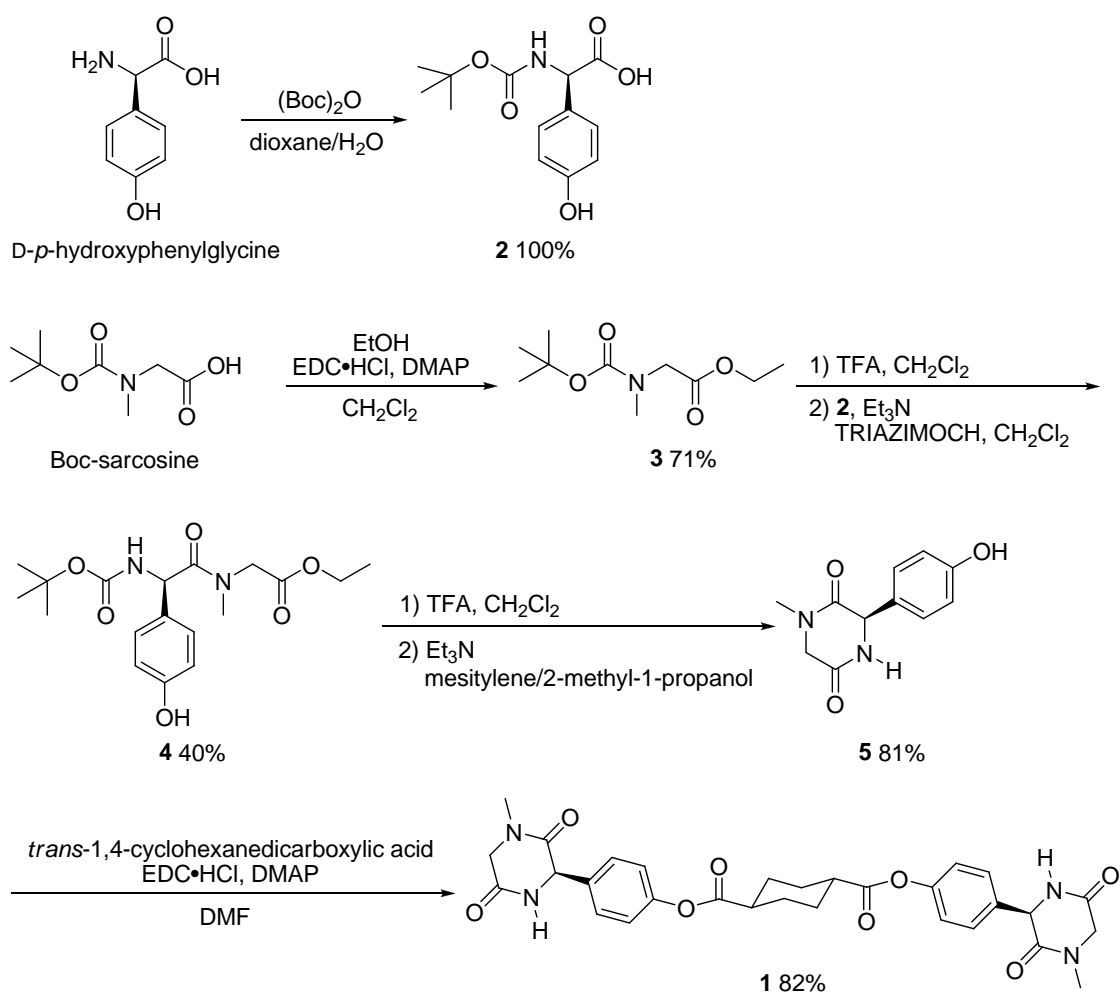
Results and Discussion

Synthesis and Properties of 1. The author had designed DKP–linker–DKP type compounds having DKP moieties at the both termini to construct supramolecular structures. The author selected *D*-*p*-hydroxyphenylglycine as one component of DKP, because it is commercially available and has hydroxy group, which is connectable to a linker part. Serine and threonine also have hydroxy group and satisfy this demand, but it is considered that phenylene spacer between the hydroxy group and chiral center of *D*-*p*-hydroxyphenylglycine is rigid compared with methylene and methine spacers of serine and threonine. Consequently, use of *D*-*p*-hydroxyphenylglycine seems to be more effective for constructing regulated structures. The author first tried to synthesize unsymmetrical DKPs from *D*-*p*-hydroxyphenylglycine with several amino acids such as glycine, alanine, and leucine, but the formed compounds were poorly soluble in organic solvents, and it was difficult to purify and isolate them. The author resolved the solubility problem by employing sarcosine (*N*-methylglycine) as another component. As the result, the author could obtain a highly pure solvent-soluble diketopiperazine **5** (Scheme 1). *N*-Monomethylation was truly effective to enhance the solubility. The author then tried to synthesize DKP–linker–DKP compounds with various linkers including xylylene, phenyleneethynylene, phenylenesilylene, and ethylenesilylene, but could not obtain the target compounds with sufficient purities. Compound **1** having *trans*-1,4-cyclohexanedicarboxylate linker could be synthesized

in the present study.

Scheme 1 illustrates the synthetic route for **1**. The amino group of D-*p*-hydroxyphenylglycine was protected with Boc to obtain **2**, and it was submitted to condensation with sarcosine ethyl ester, which was prepared by ethyl esterification of *N*-(*tert*-butoxycarbonyl)sarcosine (Boc-sarcosine) followed by Boc cleavage with trifluoroacetic acid (TFA). TRIAZIMOCH {4-[4,6-dimethoxy-1,3,5-triazin-2-yl]-4-methylmorpholinium chloride} was used as a condensation agent to avoid ester formation between the carboxy and hydroxy groups of **2**. TRIAZIMOCH can selectively react with amine to form amide with carboxylic acid in the presence of

Scheme 1



alcohol.⁸ Then the terminal Boc group of formed dipeptide **4** was removed with TFA, and the resulting TFA salt was heated in the presence of triethylamine in mesitylene/2-methyl-1-propanol. The intramolecular ester-amide exchange releasing ethanol satisfactorily proceeded to give diketopiperazine **5** in a high yield (81%). Diketopiperazine **5** was obtained as precipitate during the reaction. The purity of **5** was high enough. It is considered that the precursor *N*-nonprotected linear dipeptide was completely soluble in the solvent, while **5** was slightly soluble in mesitylene/2-methyl-1-propanol mixed solvent. Diketopiperazine **5** was soluble in DMF and DMSO. Subsequently, **1** was synthesized by the condensation of *trans*-1,4-cyclohexanedicarboxylic acid with two equivalents of **5** using EDC•HCl as a condensation agent in the presence of DMAP.

Self-assembled Structure of 1. Compound **1** was insoluble in common organic solvents except DMSO, although one amide N–H group was methylated for enhancing the solubility. The author measured the circular dichroism spectra of a solution of **1** in DMSO to examine the possibility of formation of a chiral supramolecular structure, but could not observe a Cotton effect at all. DMSO possibly breaks hydrogen bonding between the amide groups of **1** to prevent them from association. The author then examined the morphology of **1** in the solid state by AFM. Figure 1 shows the AFM image of a silicon substrate coated with a solution of **1** in DMSO. It exhibited circular objects together with a fibrous structure by their assembling. Judging from the size (diameter: 10.4 nm, height: 1.0 nm) of the circular structure, it seems that molecules of **1** aggregated on a silicon surface during the process of DMSO evaporation.

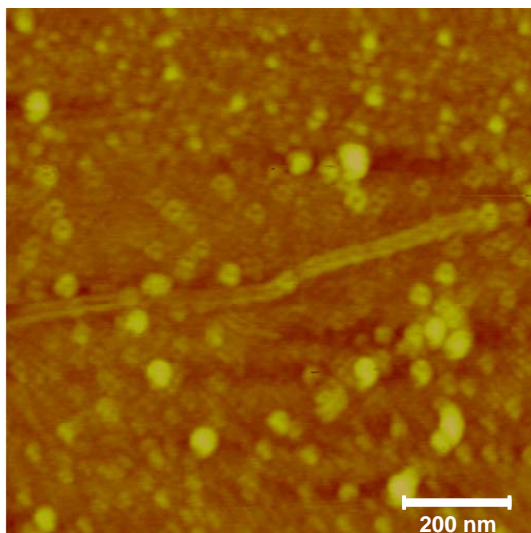


Figure 1. AFM image of **1** coated on a silicon wafer from a 0.2 w/v% solution in DMSO.

Considering the spread symmetrical structure of **1** having DKP moieties at the both termini, it is likely that **1** forms intermolecular hydrogen bonding between the DKP moieties to construct cyclic supramolecules observed in the AFM. To elucidate this assumption, the author modeled supramolecular structures consisting of 2–16 units of **1**, wherein hydrogen bonding exists between the DKP moieties. Figure 2 plots the potential energy per unit and diameter of the ring structure calculated with the molecular mechanics method using the MMFF94 force field.⁹ The author postulated that the dimer would aggregate in a linear fashion and that the trimer and the tetramer would aggregate based on a single-strand of hydrogen bonding between DKP moieties to form the ring structures. Oligomers consisting of five and more units would aggregate based on double-strands of hydrogen bonding to form cyclic structures. The energy per one unit gradually decreased with the increment of unit number (n), and became saturated around $n = 5$. The diameter of the ring increased in proportion to n . The diameter of 10.4 nm corresponded with a ring consisting of 14 molecules of **1** as illustrated in Figure 3, whose height was calculated to be 1.1 nm. The value

was coincident with the value (1.0 nm) observed by AFM. Consequently, these data suggest that the AFM-observed ring structure is cyclic 14-mer of **1** aggregated by intermolecular hydrogen bonding between the terminal DKP moieties.

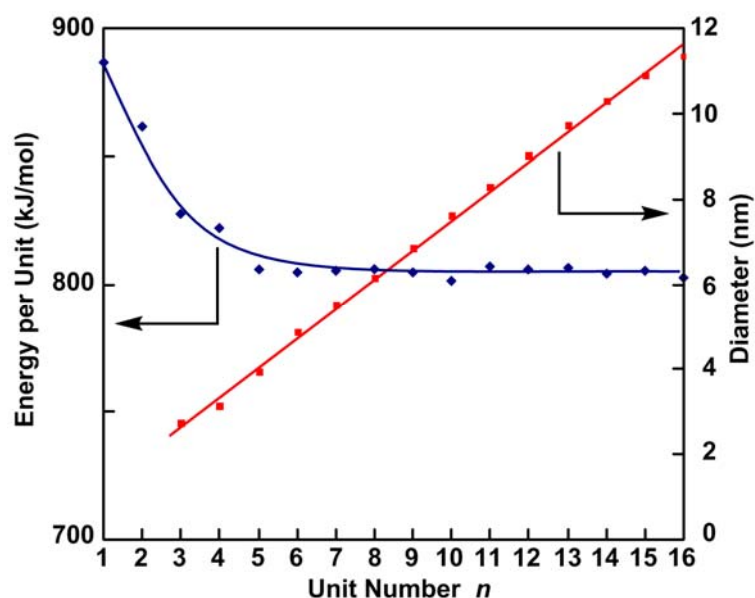


Figure 2. Unit number vs. energy per one unit and diameter of cyclic supramolecules of **1**.

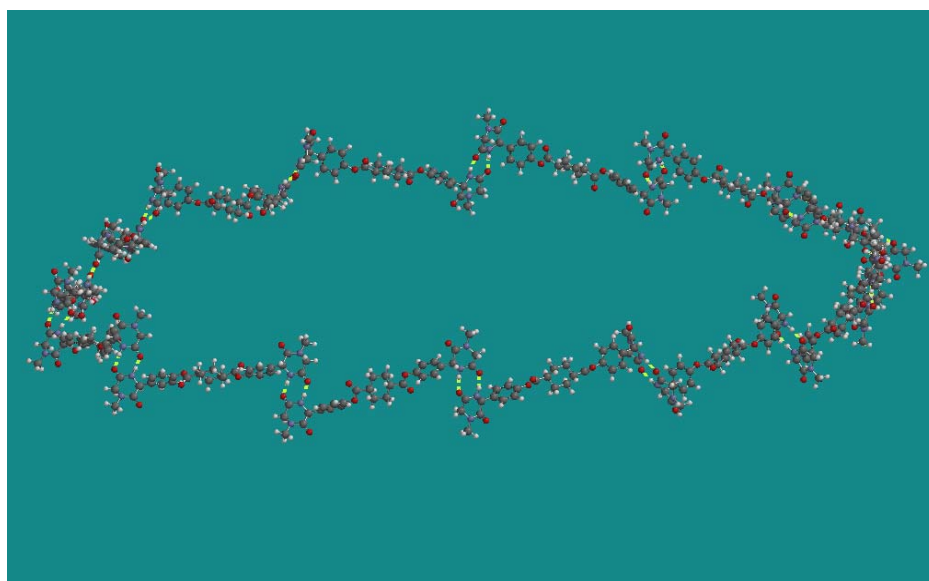


Figure 3. Cyclic 14-mer of **1** optimized by the molecular mechanics calculation. Green dotted lines represent hydrogen bonds between the DKP amide moieties.

Conclusion

The author has demonstrated the synthesis of novel compound **1** having two DKPs consisting of D-*p*-hydroxyphenylglycine and sarcosine. AFM measurement and molecular mechanics calculations suggested that **1** formed cyclic supramolecular structures based on intermolecular hydrogen bonding between the terminal DKP moieties on silicon surface. It is expected that further molecular design of a linker tethering two DKPs leads to variation of supramolecular structures.

Experimental Section

Measurements. ^1H and ^{13}C NMR spectra were recorded on a JEOL EX-400 spectrometer. Melting points (mp) were measured on a Yanaco micro melting point apparatus. Specific rotations ($[\alpha]_D$) were measured on a JASCO DIP-100 digital polarimeter with a sodium lamp as a light source. Elemental analysis was done at the Microanalytical Center of Kyoto University. Mass spectra were measured on a JEOL JMS-HX110A mass spectrometer. A sample for AFM measurement was prepared by dropping a solution of **1** in DMSO (0.2 w/v%) on a silicon substrate, followed by washing with DMSO and drying *in vacuo*. Prior to preparation of the sample, the silicon substrate was treated with a fresh piranha solution at 100 °C for 1 h to form clean silicon oxide surface, followed by extensive rinsing with deionized water, and then dried under nitrogen flow. A Nanoscope III (Digital Instruments, Inc.) was used for tapping-mode AFM to observe phase and height images.

Materials. All the reagents in monomer synthesis were used as purchased without purification. DMF was distilled over calcium hydride.

Synthesis of 1,4-*trans*-bis[cyclo(D-*p*-phenylglyciny)sarcosinyl]cyclohexane dicarboxylate (1). *N*-(*tert*-Butoxycarbonyl)-D-*p*-hydroxyphenylglycine (2) Triethylamine (11 mL, 79.0 mmol) was added to a mixture of

D-*p*-hydroxyphenylglycine (8.84 g, 52.9 mmol) and di-*tert*-butyl dicarbonate [(Boc)₂O, 11.5 g, 52.9 mmol] in dioxane/H₂O (70 mL/70 mL) at 0 °C, and the reaction mixture was stirred at room temperature overnight. H₂O (100 mL) was added to the resulting mixture, and then it was washed with ethyl acetate. The aqueous layer was acidified with 2 M HCl to pH 2, and then extracted with ethyl acetate. The organic layer was dried with anhydrous MgSO₄ and concentrated on a rotary evaporator to obtain **2** as a yellow solid quantitatively. ¹H NMR (400 MHz, CDCl₃): δ 1.40 [s, 9H, –OC(CH₃)₃], 5.02 [s, 1H, >NCH<], 5.19 [s, 1H, –ArOH], 5.73 [s, 1H, –NH–], 6.70–7.16 [m, 4H, Ar], 8.28 [br, 1H, –OH].

***N*-(*tert*-Butoxycarbonyl)sarcosine ethyl ester (3)**

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC•HCl, 19.2 g, 100 mmol), 4-(dimethylamino)pyridine (DMAP, 1.22 g, 9.99 mmol), and ethanol (10 mL, 171 mmol) were added to a solution of *N*-(*tert*-butoxycarbonyl)sarcosine (18.9 g, 99.9 mmol) in CH₂Cl₂ (500 mL) at 0 °C, and then the resulting mixture was stirred at room temperature overnight. Then, CH₂Cl₂ was distilled off using a rotary evaporator, and the residue was dissolved in ethyl acetate. It was washed with 0.5 M HCl, saturated NaHCO₃ aq., and saturated NaCl aq., and then dried over anhydrous MgSO₄. Ethyl acetate was evaporated off to obtain **3** as a colorless liquid in 71% yield. ¹H NMR (400 MHz, CDCl₃): δ 1.27, 1.29 [s, 3H, –CH₂CH₃], 1.43, 1.47 [s, 9H, –OC(CH₃)₃], 2.92, 2.94 [s, 3H, >NCH₃], 3.88, 3.97 [s, 2H, >NCH₂–], 4.20 [s, 2H, –OCH₂–].

***N*-(*tert*-Butoxycarbonyl)-D-*p*-hydroxyphenylglycinylsarcosine ethyl ester (4)**

Trifluoroacetic acid (TFA, 15.0 mL, 202 mmol) was added to a solution of **3** (8.43 g, 38.8 mmol) in CH₂Cl₂ (100 mL) at 0 °C, and the reaction mixture was stirred at room temperature overnight. After confirming the complete consumption of **3** by TLC, CH₂Cl₂ and TFA were distilled off *in vacuo*. The residual viscous liquid was

dissolved in ethyl acetate/CH₂Cl₂ (200 mL/100 mL). Triethylamine (17 mL, 122 mmol), 4-[4,6-Dimethoxy-1,3,5-triazin-2-yl]-4-methylmorpholinium chloride (TRIAZIMOH, Tokuyama Co., 12.6 g, 38.8 mmol), and **2** (13.4 g, 50.1 mmol) were added to the solution at 0 °C, and the resulting mixture was stirred at room temperature overnight. The resulting mixture was concentrated on a rotary evaporator, and then the residual viscous liquid was dissolved in CH₂Cl₂ (150 mL). It was washed with 0.5 M HCl, saturated NaHCO₃ aq., and saturated NaCl aq., and then dried over anhydrous MgSO₄. CH₂Cl₂ was evaporated off, and the residual mass was purified by recrystallization from hexane/ethyl acetate (1/2, volume ratio) to obtain **4** as a colorless solid in 40%. Mp 155–161 °C. ¹H NMR (400 MHz, CDCl₃): δ 1.24 [t, *J* = 6.8 Hz, 3H, –CH₂CH₃], 1.41 [s, 9H, –OC(CH₃)₃], 2.93, 3.01 [s, 3H, >NCH₃], 3.88, 4.34 [d, *J* = 8.8 Hz, 2H, >NCH₂–], 5.54, 5.92 [d, *J* = 4.0 Hz, 1H, >NCH<], 7.01 [s, 1H, –ArOH], 7.14 [d, *J* = 4.4 Hz, 1H, –NH–], 6.74–7.23 [m, 4H, Ar]. ¹³C NMR (100 MHz, CDCl₃): δ 14.07 [CH₃CH₂–], 28.32 [(CH₃)₃C–], 36.29 [>NCH₃], 50.09 [>NCH₂–], 54.67 [>NCH<], 61.38 [CH₃CH₂–], 80.01 [(CH₃)₃C–], 115.86, 128.35, 129.19, 155.25 [Ar], 156.35 [–OCONH–], 168.87[>CHCON<], 171.32[–CH₂COO–]. Anal. Calcd for C₁₈H₂₆N₂O₆: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.87; H, 7.12; N, 7.52.

cyclo(D-*p*-HydroxyphenylglycinyI-sarcosinyI) (5) TFA (11 mL, 148 mmol) was added to a solution of **4** (5.54 g, 15.1mmol) in CH₂Cl₂ (100 mL) at 0 °C, and the reaction mixture was stirred at room temperature overnight. After confirming the complete consumption of **4** by TLC, CH₂Cl₂ and TFA were distilled off *in vacuo*. The residual viscous liquid was dissolved in mesitylene/2-methyl-1-propanol (2/1, volume ratio), and then triethylamine (5.00 mL, 35.9 mmol) was added to the resulting solution. The resulting mixture was heated to 110 °C and stirred for 11 hours. After standing to cool to room temperature, a white solid precipitated was separated by

filtration to obtain **5** as a colorless solid in 81%. Mp (decomposed at 250–257 °C). $[\alpha]_D = -41.4^\circ$ ($c = 0.10$ g/dL, methanol). ^1H NMR (400 MHz, DMSO- d_6): δ 2.80 [s, 3H, >NCH₃], 3.87, 4.11 [d, $J = 8.8$ Hz, 2H, >NCH₂–], 4.79 [s, 1H, >NCH<], 6.72–7.11 [m, 4H, Ar], 8.59 [s, 1H, –NH–] 9.48 [s, 1H, –ArOH]. ^{13}C NMR (100 MHz, DMSO- d_6): δ 33.16 [>NCH₃], 50.96 [>NCH₂–], 58.10 [>NCH<], 115.18, 127.97, 129.47, 157.06 [Ar], 164.77[–CH₂CO–], 164.96[>NCO–]. Anal. Calcd for C₁₁H₁₂N₂O₃: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.80; H, 5.53; N, 12.68. HRMS (M^+). Calcd for C₁₁H₁₂O₃N₂ (m/z) 220.0848. Found: 220.0847.

1 EDC•HCl (959 mg, 4.99 mmol), 4-(dimethylamino)pyridine (DMAP, 61.0 mg, 0.499 mmol), *trans*-1,4-cyclohexanedicarboxylic acid (431 mg, 2.50 mmol) were added to a solution of **5** (1.10 g, 4.99 mmol) in DMF (90 mL) at 0 °C and the resulting mixture was stirred at room temperature overnight. The precipitate formed was separated by filtration and washed with H₂O and methanol to obtain **1** as a colorless solid in 82%. Mp (decomposed at 225–227 °C). ^1H NMR (400 MHz, DMSO- d_6): δ 1.57–2.64 [m, 8H, –C₆H₁₀–], 2.82 [s, 6H, >NCH₃], 4.04 [d, $J = 9.3$ Hz, 4H, >NCH₂–], 4.99 [s, 2H, >NCH<], 7.11–7.38 [m, 8H, Ar], 8.71 [s, 2H, –NH–]. ^{13}C NMR (100 MHz, DMSO- d_6): δ 27.37 [>CH(C₂H₄)₂CH<], 33.24 [>NCH₃], 41.43 [>CH(C₂H₄)₂CH<], 50.95 [>NCH₂–], 58.06 [>NCH<], 121.86, 128.20, 136.73, 150.17 [Ar], 164.28[–CH₂CO–], 164.97[>NCO–], 173.61 [–OCO–]. HRMS (M^+). Calcd for C₃₀H₃₂O₈N₄ (m/z) 577.2298. Found: 577.2296.

Molecular Mechanics Calculation. The molecular mechanics calculation was carried out with Wavefunction Inc., Spartan '06 Windows, using the MMFF94 forcefield.

References

- (1) (a) Du, Y.; Creighton, C. J.; Tounge, B. A.; Reitz, A. B. *Org. Lett.* **2004**, *6*, 309.

- (b) Lyssenko, K. A.; Lenev, D. A.; Kostyanovsky, R. G. *Tetrahedron* **2002**, *58*, 8525. (c) Palacin, S.; Chin, D. N.; Simanek, E. E.; MacDonald, J. C.; Whitesides, G. M.; McBride, M. T.; Palmore, G. T. R. *J. Am. Chem. Soc.* **1997**, *119*, 11807. (d) Chin, D. N.; Palmore, T. R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 2115. (e) Jagadosh, B.; Carducci, M. D.; Bosshard, C.; Günter, P.; Margolis, J. I.; Williams, L. J.; Mash, E. A. *Cryst. Growth Des.* **2003**, *3*, 811.
- (2) Kloster, R. A.; Carducci, M. D.; Mash, E. A. *Org. Lett.* **2003**, *5*, 3683.
- (3) Bergeron, R. J.; Phanstiel IV, O.; Yao, G. W.; Milstein, S.; Weimar, W. R. *J. Am. Chem. Soc.* **1994**, *116*, 8479.
- (4) (a) Yang, Y.; Suzuki, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Chem. Commun.* **2004**, 1332. (b) Hanabusa, K.; Mastumoto, M.; Kimura, M.; Kakehi, A.; Shirai, H. *J. Colloid Interface Sci.* **2000**, *224*, 231. (c) Hanabusa, K.; Fukui, H.; Suzuki, M.; Shirai, H. *Langmuir* **2005**, *21*, 10383.
- (5) Terada, K.; Sanda, F.; Masuda, T. *J. Macromol. Sci., Part A: Pure & Appl. Chem.* **2007**, *44*, 789.
- (6) Terada, K.; Berda, E. B.; Wagener, K. B.; Sanda, F.; Masuda, T. *Macromolecules* **2008**, *41*, 6041.
- (7) Ohta, Y.; Terada, K.; Masuda, T.; Sanda, F. in preparation.
- (8) Kunishima, M.; Kawachi, C.; Hioki, K.; Terao, R.; Tani, S. *Tetrahedron* **2001**, *57*, 1551.
- (9) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490.

List of Publications

Chapter 1

“Synthesis, Chiroptical Properties, and pH-Responsibility of Aspartic Acid- and Glutamic Acid-Based Helical Polyacetylenes”

Sanda, F.; Terada, K.; Masuda, T.

Macromolecules **2005**, *38*, 8149–8154.

Chapter 2

“Synthesis and Secondary Structure of Polyacetylenes Carrying Diketopiperazine Moieties. The First Example of Helical Polymers Stabilized by *s-cis* Amide-Based Hydrogen Bonding”

Terada, K.; Sanda, F.; Masuda, T.

under preparation

Chapter 3

“Enantioselective Reduction of Aromatic Ketimines in the Presence of Helical Polymer as Polymer Catalyst”

Terada, K.; Sanda, F.; Masuda, T.

under preparation

Chapter 4

“Polycondensation of Diketopiperazine-based Dicarboxylic Acids with Diamines and Dibromoxylenes”

Terada, K.; Sanda, F.; Masuda, T.

J. Macromol. Sci., Part A: Pure & Appl. Chem. **2007**, *44*, 789–794.

Chapter 5

“ADMET Polycondensation of Diketopiperazine-based Dienes. Polymerization Behavior and Effect of Diketopiperazine on the Properties of the Formed Polymers”

Terada, K.; Berda, E. B.; Wagener, K. B.; Sanda, F.; Masuda, T.

Macromolecules **2008**, *41*, 6041–6046.

Chapter 6

“Diketopiperazine Supramolecule Derived from Hydroxyphenylglycine”

Ohta, Y.; Terada, K.; Sanda, F.; Masuda, T.

under preparation

Chapter 7

“Synthesis of Novel Diketopiperazine-derivative and Observation of Self-assembled Structure”

Ohta, Y.; Terada, K.; Sanda, F.; Masuda, T.
under preparation

Other Publications Not Included in This Thesis

“Synthesis and Polymerization of Optically Active *N*-Propargylphosphonamides: A Novel Helical Polymer Carrying a P-Chiral Center”

Yue, D.; Fujii, T.; Terada, K.; Tabei, J.; Shiotsuki, M.; Sanda, F.; Masuda, T.
Macromol. Rapid. Commun. **2006**, 27, 1460–1464.

“Ring-Opening Metathesis Polymerization of Amino Acid-Functionalized Norbornene Derivatives”

Sutthasupa, S.; Terada, K.; Sanda, F.; Masuda, T.
J. Polym. Sci., Part A: Polym. Chem. **2006**, 44, 5337–5343.

“Ring-Opening Metathesis Polymerization of Amino Acid-Functionalized Norbornene Diester Monomers”

Sutthasupa, S.; Terada, K.; Sanda, F.; Masuda, T.
Polymer **2007**, 48, 3026–3032.

“Synthesis and Helicity of Optically Active Poly(*N*-propargylphosphonamides) Having Chiral Phosphorus Center”

Yue, D.; Fujii, T.; Terada, K.; Tabei, J.; Shiotsuki, M.; Sanda, F.; Masuda, T.
J. Polym. Sci., Part A: Polym. Chem. **2007**, 45, 1515–1524.

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